No. 17-290	
Title:	**Merck Sharp & Dohme Corp., Petitioner** **v.** **Doris Albrecht, et al.**
Docketed:	August 24, 2017
Linked with 16A1264	
Lower Ct:	United States Court of Appeals for the Third Circuit
Case Numbers:	(14-1900)
Decision Date:	March 22, 2017
Rehearing Denied:	April 24, 2017
Questions Presented	

DATE	PROCEEDINGS AND ORDERS
Jun 23 2017	Application (16A1264) to extend the time to file a petition for a writ of certiorari from July 23, 2017 to August 22, 2017, submitted to Justice Alito.
Jun 27 2017	Application (16A1264) granted by Justice Alito extending the time to file until August 22, 2017.
Aug 22 2017	Petition for a writ of certiorari filed. (Response due September 25, 2017)
Aug 31 2017	Waiver of right of respondents Affronti, Joanne, et al. to respond filed.
Sep 11 2017	Blanket Consent filed by Petitioner, Merck Sharp & Dohme Corp. on 09/12/2017
Sep 19 2017	Waiver of right of respondents Esther Parker & Pamela Paralikis to respond filed.
Sep 20 2017	Blanket Consent filed by Respondents, Albrecht, Doris, et al. on 09/21/2017
Sep 21 2017	Order extending time to file response to petition to and including October 25, 2017, for all respondents.
Sep 22 2017	Because Justice Alito now realizes that he should have recused himself from consideration of this application, the order of June 27, 2017, is vacated. Pursuant to Rule 22.2, the application (16A1264) to extend the time to file a petition for a writ of certiorari from July 23, 2017 to August 22, 2017, has been submitted to Justice Sotomayor.

Sep 22 2017	Application (16A1264) granted by Justice Sotomayor extending the time to file until August 22, 2017. (Justice Alito is recused)
Sep 25 2017	Brief amicus curiae of Pharmaceutical Research and Manufacturers of America filed.
Sep 25 2017	Brief amici curiae of Product Liability Adisory Council, Inc., et al. filed.
Oct 25 2017	Brief of respondents Doris Albrecht, et al. in opposition filed.
Nov 08 2017	DISTRIBUTED for Conference of 12/1/2017.
Nov 08 2017	Reply of petitioner Merck Sharp & Dohme Corp. filed. (Distributed)
Dec 04 2017	The Solicitor General is invited to file a brief in this case expressing the views of the United States. Justice Alito took no part in the consideration or decision of this petition.
May 22 2018	Brief amicus curiae of United States filed (to be corrected and reprinted).
May 22 2018	Brief amicus curiae of United States filed (Corrected brief received 5/29/18). **Main Document** **Proof of Service** **Other**
Jun 05 2018	DISTRIBUTED for Conference of 6/21/2018.
Jun 05 2018	Supplemental brief of respondents Doris Albrecht, et al. filed. (Distributed) **Main Document** **Certificate of Word Count** **Proof of Service**
Jun 07 2018	Supplemental brief of petitioner Merck Sharp & Dohme Corp. filed. (Distributed) **Main Document** **Certificate of Word Count** **Proof of Service**
Jun 27 2018	DISTRIBUTED for Conference of 6/27/2018.
Jun 28 2018	Petition GRANTED. Justice Alito took no part in the consideration or decision of this petition.
Jul 27 2018	Motion for an extension of time to file the opening briefs on the merits granted. The time to file the joint appendix and petitioner's brief on the merits is extended to and including September 13, 2018. The time to file respondents' brief on the merits is extended to and including November 14, 2018.
Jul 27 2018	Motion for an extension of time to file the opening briefs on the merits filed.

	Main Document
Sep 12 2018	Blanket Consent filed by Respondents, Doris Albrecht, et al.. **Blanket Consent**
Sep 13 2018	Brief of petitioner Merck Sharp & Dohme Corp. filed. **Main Document** **Certificate of Word Count** **Proof of Service**
Sep 13 2018	Joint appendix (2 volumes) filed. (Statement of costs filed) **Main Document** **Main Document** **Proof of Service**
Sep 17 2018	Blanket Consent filed by Petitioner, Merck Sharp & Dohme Corp.. **Blanket Consent**
Sep 20 2018	Brief amicus curiae of Washington Legal Foundation filed. **Main Document** **Certificate of Word Count** **Proof of Service**
Sep 20 2018	Brief amici curiae of Product Liability Adisory Council, Inc., et al. filed. **Main Document** **Certificate of Word Count** **Proof of Service**
Sep 20 2018	Brief amici curiae of Pharmaceutical Research and Manufacturers of America, et al. filed. **Main Document** **Certificate of Word Count** **Proof of Service**
Sep 20 2018	Brief amicus curiae of United States filed. **Proof of Service** **Main Document**
Oct 12 2018	Motion of the Acting Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument filed. **Proof of Service** **Main Document**
Oct 26 2018	Justice Alito is no longer recused in this case.
Nov 14 2018	Brief of respondents Doris Albrecht, et al. filed. **Main Document** **Certificate of Word Count** **Proof of Service**
Nov 21 2018	Brief amicus curiae of Public Citizen filed. **Main Document** **Certificate of Word Count** **Proof of Service**
Nov 21 2018	Brief amici curiae of Commonwealth of Virginia, et al. filed. **Main Document** **Proof of Service** **Certificate of Word Count**
Nov 21 2018	Brief amici curiae of Joseph Lane, M.D., and Vincent Vigorita, M.D. filed. **Main Document** **Certificate of Word Count** **Proof of Service**
Nov 21 2018	Brief amici curiae of MedShadow Foundation, et al. filed. **Main Document** **Certificate of Word Count** **Proof of Service**

Nov 21 2018	Brief amicus curiae of The Cato Institute filed. **Main Document** **Certificate of Word Count** **Proof of Service**
Nov 21 2018	Brief amici curiae of Tort Law Professors John C. P. Goldberg and Benjamin C. Zipursky filed. **Main Document** **Certificate of Word Count** **Proof of Service**
Nov 21 2018	Brief amici curiae of Public Law Scholars filed. **Main Document** **Certificate of Word Count** **Proof of Service** **Other**
Nov 21 2018	Brief amici curiae of Jerome P. Kassirer, M.D., et al. filed. **Main Document** **Certificate of Word Count** **Proof of Service**
Nov 21 2018	Brief amicus curiae of American Association for Justice filed. **Main Document** **Certificate of Word Count** **Proof of Service**
Nov 28 2018	SET FOR ARGUMENT ON Monday, January 7, 2019
Nov 30 2018	CIRCULATED
Dec 03 2018	Motion of the Acting Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument GRANTED.
Dec 11 2018	Record requested from the U.S.C.A. 3rd Circuit.
Dec 14 2018	Reply of petitioner Merck Sharp & Dohme Corp. filed. (Distributed) **Main Document** **Certificate of Word Count** **Proof of Service**
Dec 18 2018	Record received from the U.S.C.A. 3rd Circuit is electronic.
Dec 18 2018	Record from the U.S.D.C. District of New Jersey is electronic and located on PACER.
Jan 07 2019	Argued. For petitioner: Shay Dvoretzky, Washington, D. C.; and Malcolm L. Stewart, Deputy Solicitor General, Department of Justice, Washington, D. C. (for United States, as amicus curiae.) For respondents: David C. Frederick, Washington, D. C.

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RECORD AND BRIEFS

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OFFICE OF THE CLERK
SUPREME COURT, U.S.

17-290

No. 17-___

IN THE
Supreme Court of the United States

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

DORIS ALBRECHT, ET AL.,
Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Third Circuit

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

In *Wyeth v. Levine*, 555 U.S. 555 (2009), this Court held that the FDA's approval of a drug label does not, standing alone, insulate the manufacturer from failure-to-warn liability under state tort law. At the same time, the Court recognized that if "the FDA would not have approved" the label demanded by state law, then the manufacturer could invoke an "impossibility" preemption defense. *Id.* at 571.

In this case, it was "undisputed" that (i) "the FDA was aware of the possible link" between petitioner's drug and the risk at issue; (ii) petitioner "submitted a comprehensive safety update to the FDA reporting ... numerous studies" finding "such an association"; (iii) petitioner "proposed warning language" about this risk, but the FDA "rejected" it; (iv) the FDA stated that the "conflicting nature of the literature d[id] not provide a clear path forward" and that it needed "more time" to consider "the issue of a precaution"; and (v) only later, after a report from a task force, did the FDA become "confident" that an association "potentially" existed. Pet.App.59a-60a.

The Third Circuit nonetheless held that a jury could find that petitioner had not shown by "clear and convincing evidence" that the FDA would have rejected a warning label of the type that respondents claim state law required. *See* Pet.App.37a, 56a-57a.

The question presented is: Is a state-law failure-to-warn claim preempted when the FDA rejected the drug manufacturer's proposal to warn about the risk after being provided with the relevant scientific data; or must such a case go to a jury for conjecture as to *why* the FDA rejected the proposed warning?

PARTIES TO THE PROCEEDING AND RULE 29.6 STATEMENT

Petitioner is Merck Sharp & Dohme Corporation, a wholly owned subsidiary of the entity formerly known as Schering Plough Corporation, which has been renamed Merck & Co., Inc. No publicly held corporation owns 10% or more of the stock of Merck & Co., Inc.

Respondents—identified by name and Third Circuit docket number in Appendix G (Pet.App.203a-224a)—are more than 500 plaintiffs who brought state-law failure-to-warn claims against Merck, alleging that they were injured by Merck's drug Fosamax prior to September 14, 2010. The Third Circuit resolved their appeals in one consolidated opinion. Pet.App.1a n.*. Pursuant to this Court's Rule 12.4, Merck files this consolidated petition to challenge the Third Circuit's decision.

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73 Fed. Reg. 49603 (Aug. 22, 2008) 5

INTRODUCTION

Wyeth v. Levine, 555 U.S. 555 (2009), rejected an argument that the FDA's mere approval of a drug's label immunizes the manufacturer from any state tort liability for failure to warn. Rather, only if the FDA would have *rejected* a warning should the manufacturer be shielded from liability for failure to give it. In the latter scenario, it would truly be impossible to comply with both federal law (blocking the warning) and state law (mandating the warning). In *Levine*, however, there was no evidence that the FDA had paid more than "passing attention" to the risk at issue; no evidence that the drug manufacturer had provided the FDA with "evaluation or analysis" of the risk; no evidence that the manufacturer had "attempted to give the kind of warning" demanded by the plaintiff; and no evidence that the FDA had ever "made an affirmative decision" against allowing such a warning. *Id.* at 572-73.

In this case, by contrast, *each* of those factors is *undisputed*. Petitioner ("Merck") submitted data and analysis to the FDA suggesting that its Fosamax drug may be associated with certain bone fractures. Merck also proposed a warning addressing that risk. After back-and-forth, the FDA ultimately rejected the proposed addition, stating that it was not supported by the data. Pet.App.59a-61a. Despite all of this, the Third Circuit held that respondents' failure-to-warn claims were not legally preempted, because it believed that a *jury* could infer that the FDA's objection had been only to Merck's *wording*, and thus, as a "hypothetical" matter, that the agency might have approved the warning had it merely been phrased slightly differently. Pet.App.67a-68a.

Unfortunately, the decision below is not unique in its hostility to preemption. Despite *Levine*'s recognition that preemption would be appropriate if the FDA would have rejected the label demanded by the plaintiff, courts have erected a series of procedural and substantive hurdles to this defense, making it virtually impossible to establish, certainly as a matter of law. This case presents a particularly extreme illustration, with the court inventing a "clear and convincing evidence" standard exclusively for drug manufacturers, demanding "smoking gun" proof of *why* the FDA had rejected Merck's on-point warning, and leaving a lay jury to speculate about the intent of a federal regulatory authority.

This Court should grant certiorari to revive failure-to-warn branded drug preemption in the wake of the lower courts' interpretation of *Levine*. If a drug manufacturer candidly brings a risk to the FDA's attention and proposes an on-point warning, the FDA's rejection should suffice as a matter of law to preempt claims alleging failure to warn of that risk. By demanding more, courts have effectively eliminated impossibility preemption in this context: Even if manufacturers engage in good faith with the agency, propose a relevant warning, and follow the FDA's instructions, they remain on the hook based on a lay jury's psychoanalysis of *why* the agency had blocked compliance with state law. That untenable approach is of great importance, as proliferating tort suits stifle innovation, raise drug costs, undercut the FDA's role, and ultimately hurt public health. And this case is a perfect vehicle, because its undisputed facts would allow it to serve as an exemplar of when the preemption defense is legally established.

OPINIONS BELOW

The district court's opinion granting judgment to petitioner (Pet.App.113a-52a) appears at 2014 WL 1266994. The Third Circuit's decision vacating and remanding (Pet.App.1a-95a) was reported at 852 F.3d 268.

JURISDICTION

The Third Circuit entered judgment on March 22, 2017, and denied petitioner's timely motion for rehearing and rehearing en banc on April 24, 2017. *See* Pet.App.1a, 159a. On June 23, 2017, Justice Alito extended the time to file a certiorari petition until August 22, 2017. *See* No. 16A1264. This Court has jurisdiction under 28 U.S.C. § 1254(1).

PROVISIONS INVOLVED

Relevant statutory and regulatory provisions are reproduced at Pet.App.177a-202a.

STATEMENT

This case is about whether a brand-name drug manufacturer may be held liable for failure to warn about a health risk associated with its drug—even when the manufacturer brought that specific risk to the FDA's attention and proposed adding a warning about it to its label, only to have the FDA reject that proposal. The court below held that Merck *could* be liable under those circumstances. Although the FDA had rejected Merck's proposed warning and doubted that the data supported it, the Third Circuit ruled that a *jury*—speculating about hypotheticals—could find that it was *possible* that the FDA *would have* approved a warning had Merck altered its wording slightly (something the FDA never suggested).

A. Regulatory Background

Congress and the FDA have crafted a regulatory regime in which name-brand drug manufacturers and the agency work hand-in-hand to appropriately warn consumers of the risks inherent in using many beneficial medications. While "the manufacturer bears responsibility for the content of its label at all times," *Levine*, 555 U.S. at 570-71, the FDA also plays a central role in label approvals and revisions.

The FDA may approve a new drug "only if it determines that the drug in question is safe for use under the conditions of use prescribed, recommended, or suggested in [its] proposed labeling." *Mut. Pharm. Co. v. Bartlett*, 133 S. Ct. 2466, 2471 (2013). After approval, the FDA continues to monitor the drug and its label. The manufacturer must investigate and report serious, unexpected adverse events to the FDA within 15 days of receiving information about them, *see* 21 C.F.R. § 314.80(c)(1)(i), and each year it must report all "significant new information ... that might affect the safety, effectiveness, or labeling of the drug" to the agency, *id.* § 314.81(b)(2)(i).

Once a name-brand drug and its label have hit the market, there are only two ways in which that label may be revised by the manufacturer. *First*, the manufacturer may submit to the FDA a Prior Approval Supplement ("PAS"), asking for permission to change the label. *See generally id.* § 314.70(b). *Second*, through the Changes Being Effected ("CBE") regulations, a manufacturer may implement certain label changes subject to later FDA approval. *See id.* § 314.70(c)(6). Either way, the FDA's approval is required by federal law.

Because excessive warnings "could discourage appropriate use of a beneficial drug" and "decrease the usefulness and accessibility of important information by diluting or obscuring it," 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008), any revision to a label must meet specified scientific criteria. To justify a change to the "Warnings & Precautions" portion of a label, there must be "reasonable evidence of a causal association" between the drug and the health risk. 21 C.F.R. § 201.57(c)(6)(i). And to justify a change to the "Adverse Reactions" section, there must be "some basis to believe there is a causal relationship." *Id.* § 201.57(c)(7). These standards apply equally to changes brought about through the CBE process and to changes requested in a PAS. *See* 73 Fed. Reg. 49603, 49604-05 (Aug. 22, 2008).

Under statutory amendments not in force at the time of *Levine*, the agency has its own obligations too: It may not sit on its hands if it comes to believe that an existing label does not sufficiently warn against possible risks. If the FDA "becomes aware of new safety information that [it] believes should be included in the labeling of the drug," it "shall promptly notify" the manufacturer, 21 U.S.C. § 355(o)(4)(A), who must "submit a supplement proposing changes to the approved labeling" or else "detail[] the reasons why such a change is not warranted," *id.* § 355(o)(4)(B). Just as importantly, the FDA may not let disagreement between it and the manufacturer about the need for (or proper content of) new warnings stand in the way of public health. If it "disagrees with the proposed changes in the supplement or with the statement setting forth the reasons why no labeling change is necessary, the

[agency] *shall initiate discussions to reach agreement* on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes." *Id.* § 355(o)(4)(C) (emphasis added). After those discussions, the agency "may issue an order directing [the manufacturer] to make such a labeling change as the [FDA] deems appropriate to address the new safety information." *Id.* § 355(o)(4)(E).

B. Fosamax and Its Label

1. Merck's drug Fosamax prevents and treats osteoporosis in postmenopausal women. Like the other bisphosphonates whose chemical properties it shares, Fosamax works by slowing the deleterious process that occurs in the bones of post-menopausal women, thereby helping patients retain bone mass, maintain bone strength, and avoid fractures. Pet.App.5a-6a. In one study, it reduced the risk of hip, spine, and wrist fractures by roughly 50%, and the risk of all symptomatic fractures—that is, ones that cause pain—by 26%. C.A.App.1103, 1699.

By interfering with this deleterious process, however, drugs like Fosamax could "theoretically increase" the risk of very rare "atypical femoral fracture[s]"—fractures in a very specific part of the femur (just below the hip joint ("subtrochanteric") or in the long part of the thigh bone ("diaphyseal")), that occur with only minimal trauma. Pet.App.12a; C.A.App.1118. In effect, it is alleged that the drug "may inhibit microdamage repair," C.A.App.1773-74, leading to small cracks in the bone (sometimes known as "stress fractures"), which could in turn progress into full-blown atypical femoral fractures. Pet.App.7a.

2. Merck and the FDA have long worked hand-in-hand to ensure that Fosamax's label reflects the best, current state of knowledge about the possible risk of atypical femoral fractures.

When Fosamax first hit the market in the mid-1990s, the FDA did not require any warning about this risk, even though Merck's scientists and others had discussed it with the agency. Pet.App.12a-13a. Since then, Merck has continually provided the FDA with the latest information about the potential connection. *E.g.*, C.A.App.1808, 1810-1929, 1938-68, 2576-31, 2696-2960 (materials submitted by Merck).

In March 2008, Merck submitted a safety update with "over 30 pages of information regarding atypical femur fractures and suppression of bone turnover," noting that "recent publications" "implicated a link between prolonged bisphosphonate therapy and atypical low-energy non-vertebral fractures." Pet.App.14a. By June 2008, the FDA told Merck and other manufacturers that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates" and was "concerned about this developing safety signal." *Id.* Merck then "promptly complied" with a request for any further information. *Id.*

While the FDA "was analyzing Merck's data," Merck submitted a PAS proposing to add language to the Warnings & Precautions and Adverse Reactions sections of Fosamax's label, addressing the fractures that the FDA considered a "developing safety signal." *Id.* Based on nine articles and an analysis of fractures in Fosamax users, Merck contended that although it was then "not possible" to establish that Fosamax "increases the risk" of these fractures, it

was "important to include an appropriate statement" on the label to "increase physicians' awareness of possible fractures ... and allow early intervention," thereby "possibly preventing the progression to complete fracture." Pet.App.15a.

Accordingly, Merck proposed the following language for the Warnings & Precautions section:

> **Low-Energy Femoral Shaft Fracture**
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.

Pet.App.15a-16a. At the same time, Merck proposed adding "low-energy femoral shaft fracture" to the Adverse Reactions section of the label. Pet.App.16a.

3. Merck's submission kickstarted a back-and-forth with the FDA. In April 2009, an FDA official told Merck in a phone call that the FDA could "agree to add language in the Adverse Reactions section," but that Merck's "elevation of this issue to a precaution" was "prolonging review"; the FDA wanted to address the issue uniformly for "all bisphosphonates," but "the conflicting nature of the literature d[id] not provide a clear path forward." Pet.App.17a. Later that month, an FDA liaison sent Merck an email to the same effect: The "atypical fracture language" "could be approved" but "only" for the Adverse Reactions label, and Merck should "hold off" on changing the Warnings & Precautions label so that the agency and the industry could "decide on language" for a precaution, "*if it is warranted.*" Pet.App.17a-18a (emphasis added).

In May 2009, the FDA sent Merck a formal response authored by the same doctor from the April call. Pet.App.18a. The FDA approved the changes to the Adverse Reactions section—with a slight tweak in terms (Pet.App.18a)—but rejected the rest:

> While the Division agrees that atypical and subtrochanteric fractures should be added to the **ADVERSE REACTIONS, Post-Marketing Experience** subsections of the [Fosamax] labels, your justification for the proposed **PRECAUTIONS** section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been

> reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting.

Pet.App.18a-19a.

4. Almost a year later, the FDA told the public that the science had "not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures." Pet.App.19a. None of the studies up to that date had concluded "even that Fosamax use was definitively associated with atypical fractures"; instead, they suggested only a "potential[]" increase in risk or that bisphosphonates "may be associated" with such fractures. Pet.App.13a. To resolve the issue, the FDA announced that it would work with an outside task force to gather more information. Pet.App.19a.

In September 2010, that task force reported that there appeared to be an "association between long-term bisphosphonate use and atypical fractures." Pet.App.20a. In October 2010, the FDA announced that while it was "'still not clear'" whether bisphosphonates *caused* these "'unusual femur fractures,'" they "'ha[d] been predominantly reported in patients taking bisphosphonates.'" Pet.App.21a. An agency official credited the task force's report for the agency's change in view, stating that the report made it "'confident' that atypical femur fractures are 'potentially more closely related to' long-term use of bisphosphonates" than the agency "'previously had evidence for.'" *Id.* (quoting C.A.App.1396). As a result, the agency declared that it would *now* be "considering label revisions." Pet.App.20a.

In October 2010, the FDA formally directed the manufacturers to revise the "Precautions" section of their labels. It admitted that it still was "not clear" whether bisphosphonates caused the fractures, as they "also occur" in those "who have not been treated with bisphosphonates." Pet.App.21a. Nonetheless, because the fractures might be related to long-term use of the drug, the FDA ordered revised labels. Pet.App.21a-22a. Those labels note that "[a]typical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients," that patients with certain symptoms should be "evaluated to rule out a femur fracture," and that doctors should consider "[i]nterrupt[ing]" bisphosphonate use for such patients. Pet.App.22a.

C. This Litigation

1. After the FDA's action, many Fosamax users who had allegedly suffered atypical femur fractures sued Merck. Though the details varied, the plaintiffs generally alleged that Merck failed to warn about this risk. Pet.App.23a-24a. Some 1200 cases were sent to a multi-district litigation ("MDL") proceeding in the District of New Jersey. Pet.App.23a.

After holding a bellwether trial, the district court addressed the cross-cutting issue of preemption. It recognized that impossibility preemption "'is a demanding defense,'" Pet.App.168a (quoting *Levine*, 555 U.S. at 573), but held that there was "clear evidence that the FDA would not have approved a change to the Precautions section of the Fosamax label" before the September 2010 task force report. *Id.* The district court thus entered judgment for Merck on the claims of all plaintiffs who alleged injuries prior to that date. Pet.App.152a.

2. The Third Circuit vacated and remanded. It began by conceding that applying *Levine* is "not ... straightforward." Pet.App.28a. Its standard—that preemption is warranted if there is "clear evidence that the FDA would not have approved a change" to the label, 555 U.S. at 571—"is cryptic and open-ended, and lower courts have struggled to make it readily administrable." Pet.App.28a. *Levine* thus left "an anomaly in our preemption jurisprudence: the number of cases applying the clear evidence standard continues to grow, yet the clear evidence standard remains undefined." Pet.App.35a.

Without seeking any guidance from the FDA, the Third Circuit addressed this anomaly by adopting two rules. *First*, it held that *Levine*'s reference to "clear evidence" imposes a heightened standard of proof: To prevail on a preemption defense, "[t]he manufacturer must prove that the FDA would have rejected a warning not simply by a preponderance of the evidence, as in most civil cases, but by 'clear evidence,'" which the court equated with the more familiar "clear and convincing evidence" test. Pet.App.36a, 37a. The defendant must prove it is "*highly probable*" that the FDA would have rejected the change. Pet.App.37a (emphasis added).

Second, the court held that the question whether the FDA would have rejected the proposed change is one for the jury, even when the historical facts are undisputed, because the question is "counterfactual." Pet.App.54a. A manufacturer thus cannot establish the preemption defense as a matter of law, pre-trial, absent a "'smoking gun' rejection letter from the FDA" that would leave a jury no choice but to find the state-law claim preempted. Pet.App.55a.

The Third Circuit found no smoking gun here. To be sure, it saw plenty of smoke. Prior to the task force report, the FDA had expressed doubt about the evidence tying bisphosphonate use to atypical femur fractures, including in rejecting Merck's proposed warning. Pet.App.59a-61a. Respondents thus had to show that the FDA spurned Merck's proposal because of unspecified semantic concerns with Merck's *wording*, not because it doubted the underlying data or need for a warning. Pet.App.61a-62a. That is highly dubious, because the FDA *is required to* "initiate discussions to reach agreement on whether the labeling for [a] drug should be modified" if it "becomes aware of new safety information." 21 U.S.C. § 355(o)(4)(A), (C). Indeed, the FDA had done just that when it tweaked Merck's proposed Adverse Reactions language.

Although the court did not "discount the force of this evidence," it concluded that a jury could still find it less than "highly probable" that the FDA would have rejected a differently phrased label change. Pet.App.62a, 63a. In its view, a juror could conclude that the FDA's rejection was indeed all about Merck's terminology (*viz.*, its use of the term "stress fractures"), with the agency refusing—in violation of its statutory duty—to offer alternate language. Pet.App.67a. Thus, "a reasonable jury applying a heightened standard of proof *could* conclude" that the FDA would have allowed the label change. *Id.*[1]

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[1] The Third Circuit also held that the plaintiffs adequately pleaded a distinct failure-to-warn claim: that Merck should have altered the Adverse Reactions section of its label earlier than it did. Pet.App.70a. That ruling is not at issue here.

REASONS FOR GRANTING THE WRIT

In view of "[t]he importance of the pre-emption issue" to the pharmaceutical industry upon which so many rely, *Levine*, 555 U.S. at 563, this Court has granted review to correct courts' unduly narrow understandings of the doctrine, even absent any circuit conflict. *E.g.*, *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 610-11 (2011).

The Court should do the same here. The decision below illustrates the impossible position into which federal and state courts have forced brand-name drug manufacturers. Even if they cooperate with the FDA, share their safety data, and follow the agency's direction to "hold off" on adding label warnings, they *still* cannot escape costly, burdensome tort litigation complaining about those labels. Plaintiffs' lawyers, of course, can *always* dream up some "hypothetical" reason why the FDA might have rejected a proposed warning—and under the decision below, that suffices to reach a lay jury, which will be asked (case-by-case) to guess as to the reasons why the federal regulator blocked the manufacturer's state-law compliance.

This approach misunderstands *Levine*, conflicts with this Court's post-*Levine* precedents in *Mensing* and *Bartlett*, and threatens serious disruption to the cooperative relationship between the FDA and drug manufacturers. A jury's speculation about *why* the FDA blocked a manufacturer's effort to comply with state law cannot possibly defeat federal preemption. This petition is the ideal vehicle in which to lay down a legal marker for when a failure-to-warn claim *is* properly preempted in the branded drug context, and thus revive the preemption defense that courts since *Levine* have narrowed virtually out of existence.

I. THE LOWER COURTS HAVE MADE IT IMPOSSIBLE FOR BRAND-NAME DRUG MANUFACTURERS TO ESTABLISH PREEMPTION.

This Court warned in *Mensing* that preemption cannot be rendered "all but meaningless," 564 U.S. at 621, by forcing drug manufacturers to prove "counterfactual conduct of the FDA," *id.* at 623 (plurality op.). But the lower courts have defied that directive. In applying *Levine* to brand-name drugs, they have held the preemption defense out-of-reach by speculating as to counterfactuals, even when the record is clear that the FDA was aware of the risk and working with the manufacturer to address it. The decision below is the high-water mark of this trend, ruling that even though the FDA had rejected an on-point warning and cited inadequacies in the existing data, a jury could impose liability by "speculat[ing] about hypothetical scenarios" under a novel, heightened burden of proof. Pet.App.67a, 68a. All of this is quite wrong. No evidence of preemption could be more "clear" than the FDA's *actual rejection* of the warning required under state law.

A. States May Impose Liability for Failure To Warn Only If the FDA Would Have Allowed the Label Change.

This Court's leading decision on preemption for brand-name drug manufacturers is *Levine*, decided almost a decade ago. In that case, the majority held that the FDA's mere approval of a drug label did not, by itself, preempt state-law failure-to-warn liability. Rather, to show "impossibility" preemption, the drug manufacturer must show that it was *forbidden* by federal law from providing the additional warning—*i.e.*, that the FDA would have rejected it.

In *Levine*, the plaintiff successfully argued to the Vermont state courts that the label for Wyeth's drug Phenergan should have more strongly advised doctors to administer the drug indirectly through an IV-solution (the "IV-drip" method) rather than directly into the vein (the "IV-push" method). 555 U.S. at 560-63. On certiorari, this Court confronted the manufacturer's categorical contention that "the FDA's approvals [to Phenergan's labeling] provide[d] Wyeth with a complete defense" to the tort claims. *Id.* at 558. In Wyeth's view, "it would have been impossible for it to comply with the state-law duty to modify Phenergan's labeling without violating federal law," *id.* at 563, because it had no power to change its label without the FDA's permission.

The Court agreed in principle that, had federal law prevented Wyeth from updating its label, then Levine's failure-to-warn claim would have been preempted. *Id.* at 572. But the Court disagreed with that premise. The majority explained that, under the federal scheme, it is the manufacturer's duty to ensure that "its warnings remain adequate as long as the drug is on the market." *Id.* at 571. Through the CBE regulation, manufacturers may strengthen their existing warnings, even without the FDA's prior permission, provided they have good reason to do so. *See id.* at 569-71. Accordingly, the "mere fact that the FDA approved Phenergan's label" did not alone make compliance impossible, and so did not warrant preemption. *Id.* at 573; *see also id.* at 593 (Thomas, J., concurring in judgment) ("nothing in the ... regulatory scheme necessarily insulates Wyeth from liability under state law simply because the FDA has approved a particular label").

"Of course," the majority went on to admit, "the FDA retains authority to reject labeling changes," even when made "pursuant to the CBE regulation," "just as it retains such authority in reviewing all supplemental applications." *Id.* at 571. And if the FDA would have *rejected* the relevant change, that would certainly trigger preemption. *See id.* "But absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements." *Id.*

Wyeth "offered no such evidence." *Id.* at 572. *First*, Wyeth did "not argue that it supplied the FDA with an evaluation or analysis" about "the specific dangers posed by [IV-push]." *Id.* at 572-73. *Second*, the record showed that neither the FDA nor Wyeth "gave more than passing attention to the issue." *Id.* at 572. *Third*, Wyeth "d[id] not argue that it attempted to give the kind of warning required by the Vermont jury," or that it had been "prohibited from doing so by the FDA." *Id.* *Finally*, the Vermont Supreme Court "concluded that the FDA had not made an affirmative decision to preserve [IV-push]" or against "strengthening [Wyeth's] warning about IV-push." *Id.* Given this utter paucity of evidence, the majority could not "credit Wyeth's contention that the FDA would have prevented it from adding a stronger warning." *Id.*

The general rule that emerges from *Wyeth* is, in theory, administrable: If the FDA would have allowed a stronger warning, then states may impose liability for the manufacturer's failure to provide one. But if the FDA would have rejected such a change, the failure-to-warn claim is preempted. *See id.*

B. In the Absence of Further Guidance, Courts Have Gutted the Preemption Defense That *Levine* Recognized.

In practice, however, *Levine*'s line has proved elusive. This Court need not take Merck's word for it. As the court below put it, *Levine* did not "explain how courts should apply" its "cryptic," "open-ended" standard, and "lower courts have struggled to make it readily administrable." Pet.App.28a, 33a. Other courts have also observed that *Levine* did not "define clear evidence," *Reckis v. Johnson & Johnson*, 28 N.E.3d 445, 457 (Mass. 2015), or "clarify what constitutes" it, *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 391 (7th Cir. 2010). *Levine* did not indicate "the level of proof required" to demonstrate preemption, *Dobbs v. Wyeth Pharm.*, 797 F. Supp. 2d 1264, 1270 (W.D. Okla. 2011), and so "lower courts are left to determine what satisfies this 'clear evidence' standard in each case," *Schilf v. Eli Lilly & Co.*, 2010 WL 3909909, at *4 (D.S.D. Sept. 30, 2010).

In short, while *Levine* was a good illustration of a case in which the manufacturer did *not* prove that the FDA would have rejected a labeling change, it gave the lower courts little help in determining when a drug manufacturer *has* proven that proposition. Without that guidance, and in the absence of an exemplar case from which to analogize, the state and lower federal courts have gradually shifted the line further and further in tort plaintiffs' favor, against preemption and expanding liability. Left to their devices, the courts have made proving impossibility preemption under *Levine* next to impossible. The Third Circuit's decision below epitomizes that shift, rendering the defense truly academic.

1. Procedurally, courts have interpreted the *Levine* majority's offhand, solitary reference to "clear evidence," 555 U.S. at 572, as imposing a uniquely high burden of proof, beyond the difficulty inherent in proving the impossibility of complying with both state and federal law.

The Seventh Circuit, for example, read *Levine* to limit preemption to cases in which the manufacturer "met the stringent standard of proving that there was *clear evidence* the FDA would have rejected the proposed change," *Mason*, 596 F.3d at 391, and held that the manufacturer had not made the "extensive showing required by *Levine*" because it did not "meet its burden of demonstrating by *clear evidence*" that the FDA would have rejected the proposed label, *id.* at 396 (emphasis added). Massachusetts' Supreme Judicial Court followed, setting out "*clear evidence*" as the required standard, *Reckis*, 28 N.E.3d at 457; referring to it *thirteen times*; and suggesting that it requires unusually strong proof of a virtually irrebuttable character, *see, e.g.*, *id.* at 460 n.29; *see also Dobbs v. Wyeth Pharm.*, 606 F.3d 1269, 1270 (10th Cir. 2010) (mem.) (remanding for application of *Levine*'s "new 'clear evidence' standard").

Substantively, these courts have effectively eliminated *Levine*'s preemption defense, requiring a manufacturer to prove that the FDA actually denied a request for a virtually identical label—*and* that it did so because it disagreed with the proposed label *as a matter of policy*, not for some other reason—to obtain judgment as a matter of law. Since the FDA does not always spell out its reasoning, this makes it all but impossible to avoid a trial in which the jury is left to speculate about the agency's thought process.

Reckis proves the point. There, the plaintiffs claimed that ibuprofen's label should have warned them—by name or by degree of dangerousness—about the risk of the "life-threatening disease" of toxic epidermal necrolysis ("TEN") and its more serious variant, Stevens-Johnson Syndrome ("SJS"). 28 N.E.3d at 454. However, a subsequent citizen's petition (which allows citizens to ask the FDA to strengthen a drug's label, *see* 21 C.F.R. § 10.25(a)) asked the FDA to warn that ibuprofen could cause "serious skin reactions" that "may progress to more serious and potentially life-threatening diseases, including ... [SJS] and [TEN]." 28 N.E.3d at 453. In response, the FDA ordered the label revised to warn of "severe skin reactions," but not to mention the life-threatening nature of those reactions or to identify SJS or TEN by name, noting that consumers who purchase ibuprofen off the shelf are unlikely to recognize those names. *Id.* at 453.

Nonetheless, the Supreme Judicial Court held that the plaintiffs' claims were not preempted insofar as they sought a warning of life-threatening risks. *See id.* at 456-60. Even though the citizen petition had expressly requested such a warning to no avail, the court hypothesized that the agency's refusal "could well have been merely a byproduct of its rejection of these requested warnings" because they mentioned the conditions by name. *Id.* at 459. That is, perhaps the FDA *would have* approved a warning that noted the risk of life-threatening reactions but omitted their names. Because the agency "provided no reasoning" for rejecting the life-threatening aspect of the warnings, it would be "speculative" to rely on its rejection to find preclusion. *Id.*

Other decisions have been similarly dismissive. In *Mason*, for example, the Seventh Circuit found no preemption even though the FDA thrice rejected calls to add risk of suicide to the label of another antidepressant from the same chemical category, and even though the FDA publicly stated that there was no evidence of increased suicide risk in adults three months *after* the 23-year-old victim took the medicine. 596 F.3d at 394-95. And in *In re Prempro Products Liability Litigation*, the Eighth Circuit spent all of a sentence rejecting a claim that the FDA would have rejected stronger warnings. 586 F.3d 547, 563 (8th Cir. 2009); *see Mason*, 596 F.3d at 391 n.1 (noting that *Prempro* rejected preemption "rather summarily"); *see also, e.g.*, *Gurley v. Janssen Pharm., Inc.*, 113 A.3d 283, 291-92 (Pa. Super. Ct. 2015) (no preemption because the proposed but FDA-rejected warning of "possible birth defects" mentioned as an example a different congenital malformation than one at issue); *Hutto v. McNeil-PPC, Inc.*, 79 So. 3d 1199, 1210 (La. Ct. App. 2011) (no preemption because the manufacturer "did not attempt to have all the warnings" the plaintiffs requested "included on its Infants' Tylenol® label").

Indeed, even the few cases in which courts *have* found preemption illustrate the heightened barriers courts have erected around that defense. In *Cerveny v. Aventis, Inc.*, 855 F.3d 1091, 1095 (10th Cir. 2017), the plaintiffs asserted that the victim's parents should have been warned about the risk of birth defects when taking the fertility drug Clomid *prior* to pregnancy, not just *during* pregnancy. The Tenth Circuit assumed that, to prevail, Aventis had to show that "'no reasonable juror could conclude that it

[was] anything less than highly probable that the FDA would have rejected' the proposed label" in order for the manufacturer to prevail at summary judgment. *Id.* at 1099 (quoting Pet.App.59a). Aventis met that standard, but only because a prior citizen petition asking the FDA to alter Clomid's label had "presented arguments [that were] *virtually identical* to the Cervenys' [arguments]," and the FDA denied it *and* stated expressly that "the scientific literature did not justify ordering changes to the labeling that warn ... beyond those presently included." *Id.* at 1101. In other words, it is still possible to prevail on a preemption defense, but only if the FDA rejected a near-verbatim request *and* it expressly did so because it disagreed with that request as a matter of policy or science.

2. The decision below represents the high-water mark of lower courts' efforts to gut manufacturers' preemption defense, building on almost a decade of plaintiff-friendly caselaw misconstruing *Levine*.

Procedurally, the Third Circuit formalized the heightened evidentiary burden largely left implicit in cases like *Reckis*. The court squarely held that drug manufacturers "must prove that the FDA would have rejected a warning not simply by a preponderance of the evidence, as in most civil cases, but by 'clear evidence,'" a standard "synonymous" with the clear-and-convincing-evidence standard that the court called a "well-recognized intermediate standard of proof." Pet.App.35a-37a. The court defined "clear and convincing" evidence as evidence "'indicating that the thing to be proved is *highly probable* or *reasonably certain*.'" Pet.App.37a (emphases added) (quoting *Black's Law Dictionary* 674 (10th ed. 2009)).

The court further held that this standard must be applied by a jury, not by a judge. In its view, the *Levine* test requires a "counterfactual" analysis, "based on correspondence, agency statements, contemporaneous medical literature, the requirements of the CBE regulation, and whatever intuitions the factfinder may have about administrative inertia and agency decision-making processes." Pet.App.54a. The court admitted that this was a "complex" task, but concluded that "it does not require any special legal competence or training" and therefore "the question of whether the FDA would have approved a plaintiff's proposed warning is a question of fact for the jury." *Id.*

On that approach, a drug manufacturer is only entitled to judgment as a matter of law if *no* "*reasonable jury* could find it less than *highly probable* that the FDA would have rejected Plaintiffs' proposed warning." Pet.App.56a-57a (emphases added). As a practical matter, this leaves virtually no avenue for pre-trial relief, even if all the historical facts are undisputed. Absent a comprehensive, highly detailed rejection letter from the FDA, a plaintiff's lawyer could always chalk the agency's decision up to some idiosyncratic defect that the drug manufacturer could have remedied had it only tried harder or strung words together differently. And a jury, facing a sympathetic plaintiff, would not need much urging to reach such a finding, especially with the thumb that the "clear and convincing" standard places on the scales. This approach thus replaces the court, acting as gatekeeper and applying a rule of law, with a lay jury, invited to speculate case-by-case about why an expert federal agency did what it did.

The Third Circuit's heightened evidentiary standard—and its determination about the identity of the factfinder—bore fruit in its substantive result. The court acknowledged the myriad indications that the FDA would have rejected *any* additional warning about the connection between Fosamax and atypical femoral fractures before September 2010: Merck's submission of relevant data and proposed warning; the FDA's rejection and its statements asking Merck to "hold off" while it evaluated whether any warning was "warranted"; the agency's expressions of doubt about the strength of the data; and its convening of a task force, only *after* whose report the FDA ordered a label revision. Pet.App.59a-61a. All of these facts were "undisputed." *Id.*; *see supra* pp. 7-13.

The court also acknowledged the fundamentally bizarre claim at the heart of respondents' case. There was no dispute that the FDA had rejected Merck's attempt to strengthen its label. If it had done so because the agency did not believe that *any* warning was needed, then respondents' claims were plainly preempted. Their claims therefore hinged on the notion that the FDA had concluded that a stronger warning was needed regarding atypical femur fractures—in other words, that Merck had done the right thing by going to the FDA and seeking leave to amend its warning—but that the agency had inexplicably disregarded its statutory obligations and rejected Merck's supposedly deficient label outright based on a "language quibble" (Pet.App.61a), rather than work with Merck on a warning that would properly warn the public of the risk that all parties recognized (just as the agency had done for Merck's proposed Adverse Reactions label change).

Despite all of this, the court held that Merck could not satisfy the court's heightened burden of proof. It lacked the "smoking gun" needed to prevail as a matter of law because "a reasonable juror, looking at all the evidence and trying to reconstruct a hypothetical event, could conclude that it is less than highly probable that the FDA would have rejected the change." had it been "properly worded." Pet.App.56a, 62a-63a. In other words, even though the FDA *did* reject Merck's warning, the jury could conjecture about the FDA's reasoning and thereby conclude that the agency *would not have* rejected the warning had Merck improved its draftsmanship.

The upshot is this: Unless a plaintiff demands a warning nearly identical to one the FDA has already rejected—and rejected expressly on scientific rather than semantic or ambiguous grounds—state failure-to-warn claims are not preempted, no matter how hard a manufacturer tries to meet its obligations.

C. The Third Circuit's Decision Is Wrong.

On both procedure and substance, the decision below is flatly mistaken.

1. Take first its clear-and-convincing-evidence standard. In the past few years, this Court has twice reiterated that the preponderance of the evidence standard "is the standard generally applicable in civil actions, because it allows both parties to share the risk of error in roughly equal fashion." *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, 134 S. Ct. 1749, 1758 (2014); *see also id.* (entitlement to fees in patent cases need not be proven by clear and convincing evidence); *Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 136 S. Ct. 1923, 1934 (2016) (misconduct for

purposes of enhanced patent damages need not be proven by clear and convincing evidence). In keeping with this strong default rule, this Court has applied a higher standard in civil litigation only where Congress has specified one, *see, e.g.*, *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 102-06 (2011), where courts have traditionally applied one, *see, e.g.*, *Radio Corp. of Am. v. Radio Eng'g Labs., Inc.*, 293 U.S. 1, 7-9 (1934), or where the Constitution demands one, *see, e.g.*, *Addington v. Texas*, 441 U.S. 418 (1979).

Whether the FDA would have rejected a label change for purposes of a preemption defense falls into none of these categories. Congress has not spoken to the issue; the Third Circuit identified no historical practice requiring heightened proof; and the Constitution does not demand any. While the parties "may be interested intensely in [this] civil dispute over money damages," it is not unique or important enough to trigger heightened standards of proof. *Santosky v. Kramer*, 455 U.S. 745, 755 (1982).

The Third Circuit did not address this wall of countervailing authority. Instead, it dissected the single sentence on this topic in *Levine*, concluding that in context "[t]he term 'clear evidence' [must] ... specif[y] how *difficult* it will be for the manufacturer to convince the factfinder." Pet.App.35a. But "the language of a[Supreme Court] opinion is not always to be parsed as though we were dealing with the language of a statute." *Reiter v. Sonotone Corp.*, 442 U.S. 330, 341 (1979). This Court would not upend the ordinary rules of civil litigation through a single sentence, especially in a case that did not present the issue because Wyeth offered "*no* such evidence." 555 U.S. at 572 (emphasis added). Rather, the Court was

simply restating the principle that preemption requires *actual* rather than *hypothetical* conflict. *See Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 884 (2000). As *Geier* thus instructed, "a court should not find preemption too readily in the absence of *clear evidence of a conflict*." *Id.* at 885 (emphasis added). *Levine* was just invoking that lesson, not creating a unique standard of proof from whole cloth.

The Third Circuit also reasoned that the Court has often used "clear evidence" to refer to a standard of proof. Pet.App.36a. However, those cases prove only that, when the Court *does* impose a heightened standard, it does so clearly and for good reason. *See Reno v. Am.-Arab Anti-Discrimination Comm.*, 525 U.S. 471, 489 (1999) (requiring "particularly demanding" proof of selective prosecution "[b]ecause such claims invade a special province of the Executive"); *Oriel v. Russell*, 278 U.S. 358, 362-63 (1929) (calling for "clear and convincing evidence" for orders to turn over property in bankruptcy because "[t]he proceeding is one in which coercive methods by imprisonment are probable and are foreshadowed"); *Microsoft*, 564 U.S. at 101 (adopting a heightened standard because Congress used the term "presumed valid," which had a "settled meaning in the common law" stretching back centuries). *Levine*'s stray use of "clear evidence," without any explanation of the compelling need for a departure from the ordinary rules, bears no resemblance to these cases.

Finally, the Third Circuit reasoned that its heightened standard flowed from the presumption against preemption. Pet.App.37a. This Court has explained, however, that it is "unusual" to "treat a presumption as alone establishing the governing

standard of proof"; presumptions generally establish who bears the burdens of production and persuasion. *Microsoft*, 564 U.S. at 103. Contrary to the Third Circuit's fears, this view still leaves preemption a "demanding defense," Pet.App.37a (quoting *Levine*, 555 U.S. at 573); manufacturers must, after all, show it was *impossible*, not merely difficult, to comply with both state and federal law.

2. The Third Circuit went further astray when it came to application of *Levine*'s substantive rule. There could hardly be clearer evidence that the FDA *would have* rejected a warning than the undisputed fact that the FDA *did* reject a warning. Yet even that is not sufficient for the court below, which would ask a *jury* to psychoanalyze *why* the agency did so, and reject preemption based on such conjecture.

In *Levine*, the majority pointed to a series of facts that precluded Wyeth from demonstrating that the FDA would have rejected a stronger warning: Wyeth had not "supplied the FDA" with data; neither Wyeth nor the FDA "gave more than passing attention to the issue"; Wyeth had not "attempted" to give a stronger warning; and the FDA had not made "an affirmative decision" to reject one. 555 U.S. at 572-73. Although *Levine* had no occasion to spell out which combinations of these facts would suffice, here *all of them* are *undisputed*. Pet.App.46a n.122. Merck raised the issue of atypical femoral fractures with the FDA, provided the agency with all available data, proposed a relevant warning, and was told to "hold off" because its justification was "inadequate." There is thus no factual dispute for a jury to resolve. If the factors *Levine* mentioned are relevant, then there *must* be preemption here, as a matter of law.

The court reasoned, however, that a jury could find that FDA rejected Merck's proposed warning because it objected to some of its particular *language* and not because it decided—as a policy matter—that a warning was inappropriate. Pet.App.64a-66a. Thus, a the FDA may have approved a *differently worded* warning compliant with state law. *Id.*

But this sort of conjecture by an inexpert lay jury cannot possibly defeat federal preemption. As this Court's post-*Levine* decisions make clear, preemption is not overcome by an attenuated chain of remote possibilities by which the defendant, hypothetically, could have reconciled conflicting state and federal duties. The generic drug manufacturers in *Mensing*, for example, could not independently revise their own labels, but could have lobbied the FDA to work with the name-brand manufacturer on a change. 564 U.S. at 616. Even if federal law *required* them to do so, the Court held that state failure-to-warn claims were preempted: It was "certainly possible that, had the [generic] [m]anufacturers asked the FDA for help, they might have eventually been able to strengthen their warning." *Id.* at 620. But such "conjecture[]" does not "suffice" to defeat preemption; otherwise, conflict preemption would be "all but meaningless." *Id.* at 621; *see also id.* at 623 (plurality op.) ("consider[ing] ... the contingencies inherent in these cases" would be "speculati[ve]" and inappropriate). *Bartlett* recognized a similar point when it held that some possibilities of reconciling conflicting state and federal obligations—such as "simply leaving the market"—are too extreme or hypothetical to defeat the preemption defense. 133 S. Ct. at 2478.

The Third Circuit's reasoning cannot be squared with these cases. It is "certainly possible" that the FDA's rejection of a warning proposed by a brand-name manufacturer could have been based on some non-scientific objection to the warning's terminology. And so it is also "certainly possible" that the FDA might, hypothetically, have approved a warning that used different verbiage. But as *Mensing* teaches, "certainly possible" does not defeat preemption. 564 U.S. at 620. Playing this "what if" game—in this context, by nitpicking the manufacturer's proposed warning in an effort to imagine an alternative basis for its rejection by the FDA—simply takes the notion of impossibility too far, rendering preemption "all but meaningless." *Id.* at 621. And asking a lay jury to conjecture case-by-case about "counterfactual[s]" like these (Pet.App.63a) offends the Supremacy Clause. If it is undisputed that the manufacturer gave the FDA the relevant data and proposed changing its label, that should suffice—as a matter of law—to preempt state tort liability for failure to warn.

II. This Is an Ideal Vehicle To Clarify the Legal Scope of a Critical Defense in an Important Area of Law.

This Court should step in to correct the errors discussed above, because of the importance of the preemption defense to the pharmaceutical industry, and because the approach reflected by the decision below threatens the cooperative regulatory process between the FDA and drug manufacturers. And this is an ideal vehicle for doing so, because the facts here would allow this case to be an exemplar to the courts of when failure-to-warn claims *are* preempted—a counterexample to *Levine*, so to speak.

A. An Unduly Narrow Preemption Defense Threatens the Pharmaceutical Industry and the FDA's Regulatory Role.

When it comes to policing the boundary between state tort law and federal regulation of prescription drugs, this Court has recognized the overwhelming importance of getting it right. In its recent cases in this area, it has generally granted review because of the "importance of the pre-emption issue," *Levine*, 555 U.S. at 563—and sometimes based on the FDA's request—not because of disagreement amongst lower courts, *e.g.*, Pet. for a Writ of Cert. in *Mensing*, 2010 WL 638478, at *19-*25; Pet. for a Writ of Cert. in *Levine*, 2007 WL 776723, at *13-*15.

This is for good reason. Each year, tens of thousands of plaintiffs sue drug companies in tort; indeed, this MDL alone embraces over one thousand. But, extended too far, state tort law undermines the FDA's expert judgment by substituting regulation by one lay jury after another (and potentially in conflict with one another). *See Levine*, 555 U.S. at 626 (Alito, J., dissenting) (warning against allowing "juries in all 50 States ... to contradict the FDA's expert determinations"). After all, "juries are ill equipped to perform the FDA's cost-benefit-balancing function," and only the expert agency "has the benefit of the long view." *Id.* Left unchecked, moreover, state tort law risks "whipsawing the medical community," *id.*, and thus jeopardizes access to safe and affordable medicines by "rais[ing] prices to the point where those who are sick are unable to obtain the drugs they need," *id.* at 582 (Breyer, J., concurring). Both the regulatory scheme and the public interest suffer when the scale is tilted too heavily toward plaintiffs.

The decision below tilts those scales in extreme fashion, and threatens those important interests. To start, the Third Circuit's approach inevitably will increase drug prices, because it puts manufacturers in an impossible spot: Even if they disclose every potential new risk to the FDA, and even if they seek to change their labels to account for those risks, they still face liability at the hands of a jury unless the FDA gives them definitive proof that it would have rejected every conceivable proposed change as a matter of policy. Most often, however, there is no such "smoking gun."

The Third Circuit's decision also undermines the FDA's regulatory authority. The court's clear-and-convincing-evidence standard means that even where it is more likely than not that the FDA *would have rejected* the plaintiff's demanded label change, the manufacturer cannot invoke preemption. By definition, then, the Third Circuit's test applies where the FDA would have made one policy decision, but a sympathetic jury evaluating an isolated case makes another, thus transferring regulatory power from the FDA to inexpert juries and their potentially conflicting findings. No one could think that this outcome embodies wise regulatory policy.

In addition, the decision below threatens to swamp the FDA and disrupt its relationship with the industry. If any hypothetical alternative, non-scientific basis for the agency's rejection of a proposed warning suffices to defeat preemption, then manufacturers will have no choice but to inundate the agency with alternative proposals, requests for clarification, and other attempts to smoke out its precise grounds. This Court has warned, however,

against liability rules that give regulated parties "an incentive to submit a deluge of information that the [FDA] neither wants nor needs," to the detriment of the agency and the public it protects. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 (2001).

In short, the decision below will hurt not only the pharmaceutical industry, but the patients it serves and the agency that regulates its products (which has thus far not been asked to weigh in).

B. This Case Presents an Ideal Vehicle for Defining *Levine*'s Parameters.

As explained above, in the absence of guidance illustrating the kinds of facts that prove preemption under *Levine*, courts have construed the defense very narrowly, heaping up obstacles to manufacturers wishing to show that the FDA would have rejected the plaintiff's demanded label. *See supra* Part I.B.

This case presents an opportunity to turn the tide. The Third Circuit made clear that its decision turned on its interpretation of *Levine*'s statement about "clear evidence." It emphasized that the question before it was "not just whether a reasonable juror could find that the FDA would have approved [respondents'] proposed warning," but "whether a reasonable juror could find that it is *highly probable* that the FDA would have rejected the warning." Pet.App.58a (emphasis added). And it relied on that heightened standard to reverse the district court's judgment: Because a reasonable jury could "at least" conclude that it was not "highly probable" that the FDA would have "rejected [respondents'] proposed warning," summary judgment was inappropriate. Pet.App.63a; *see also, e.g.*, Pet.App.58a, 59a.

More importantly, this case would provide the Court with an excellent vehicle for putting another stake in the ground, across the field from *Levine*'s—this time to illustrate facts that *prove* preemption and to fashion an administrable rule of law that *protects* the Supremacy Clause. Merck presented compelling evidence on every front where Wyeth fell short. *See supra* p. 28. Indeed, the Third Circuit itself admitted that, even under its own heightened standard, this case was close. It did not "discount the force" of Merck's evidence about the FDA's actions, or doubt its "potential to sway a jury." Pet.App.62a. But because it demanded a "'smoking gun' rejection letter," and authorized the jury to speculate about the *basis* for the FDA's undisputed refusal to allow Merck to comply with state law, it refused summary judgment. Pet.App.55a, 67a.

If preemption does not exist as a matter of law here, it will rarely be found to exist anywhere. This Court should confirm that it does, and correct the ill-conceived course set by other courts post-*Levine*.

CONCLUSION

The petition should be granted.

AUGUST 22, 2017

Respectfully submitted,

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APPENDIX

APPENDIX A

PRECEDENTIAL

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

Nos. 14-1900 et al.*

IN RE: FOSAMAX (ALENDRONATE SODIUM)
PRODUCTS LIABILITY LITIGATION

On Appeal from the United States District Court
for the District of New Jersey
(D.C. Nos. 3:08-cv-00008-FLW *et al.*, MDL No. 2243)
District Judge: Honorable Joel A. Pisano

Argued June 30, 2016

Before: FUENTES, CHAGARES, and RESTREPO,
Circuit Judges

(Opinion Filed: March 22, 2017)

* This opinion applies to all appeals listed in Appendix A, attached.

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OPINION OF THE COURT

FUENTES, *Circuit Judge.*

Beginning in 2010, hundreds of plaintiffs filed personal-injury suits against the drug manufacturer Merck Sharp & Dohme, alleging that the osteoporosis drug Fosamax caused them to suffer serious thigh bone fractures. Each Plaintiff brought a state-law tort claim alleging that Merck failed to add an adequate warning of the risk of thigh fractures to Fosamax's FDA-approved drug label. Many Plaintiffs also brought a variety of additional claims including defective design, negligence, and breach of warranty.

Plaintiffs' suits were consolidated for pretrial administration in a multi-district litigation in the District of New Jersey. Following discovery and a bellwether trial, the District Court granted Merck's motion for summary judgment and dismissed all of Plaintiffs' claims on the ground that they were preempted by federal law. The District Court based its ruling on the Supreme Court's decision in *Wyeth v. Levine*,[1] which holds that state-law failure-to-warn claims are preempted when there is "clear evidence" that the FDA would not have approved the warning that a plaintiff claims was necessary.

We will vacate and remand. Preemption is an affirmative defense, and Merck has not carried its burden to prove that it is entitled to that defense as a matter of law. The *Wyeth* "clear evidence" standard is demanding and fact-sensitive. It requires the factfinder to predict a highly probable outcome in a

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[1] 555 U.S. 555 (2009).

counterfactual world and, therefore, requires a court sitting in summary judgment to anticipate both the range of conclusions that a reasonable juror might reach and the certainty with which the juror would reach them. Here, Plaintiffs have produced sufficient evidence for a reasonable jury to conclude that the FDA would have approved a properly-worded warning about the risk of thigh fractures—or at the very least, to conclude that the odds of FDA rejection were less than highly probable. Under *Wyeth* and Rule 56, that is enough for Plaintiffs to defeat summary judgment and proceed to trial.

I. BACKGROUND

A. Fosamax and Atypical Femoral Fractures

Fosamax is a drug manufactured by Merck that belongs to a class of drugs known as bisphosphonates. The Food and Drug Administration ("FDA") approved Fosamax in the 1990s for the treatment and prevention of osteoporosis in postmenopausal women.

Fosamax treats osteoporosis by correcting an imbalance in the so-called "bone remodeling" process. Throughout a person's life, bones are continuously broken down through a process called resorption and then reformed by the creation of new bone cells. In postmenopausal women, the rate of bone resorption exceeds that of bone formation, thereby causing bone loss. If bone loss continues unchecked, a person may develop osteoporosis, "a disease characterized by low bone mass and deterioration of bone structure that causes bone fragility and increases the risk of

fracture."[2] Bisphosphonates like Fosamax slow the resorption process, restoring the balance between resorption and formation and reducing the risk of osteoporotic fracture.

Plaintiffs claim, however, that Fosamax can actually increase the risk of certain bone fractures. They allege that by slowing resorption, bisphosphonates inhibit bone repair. According to Plaintiffs, bones frequently develop so-called "microcracks," which are ordinarily repaired through the resorption process. An accumulation of microcracks can lead to incomplete bone fractures called "stress fractures." The standalone term "stress fracture" typically connotes a fracture resulting from excessive loading of a normal bone, and is commonly seen in physically active individuals. A so-called "insufficiency stress fracture," by contrast, is a fracture caused by normal loading of poor-quality bone. Plaintiffs claim that while stress fractures typically heal on their own, "some Fosamax users who develop insufficiency fractures have reduced bone toughness, and Fosamax prevents the normal repair of the fracture."[3] According to Plaintiffs, these patients may then go on to develop what are known as "atypical femoral fractures": severe, non-traumatic, low-energy complete fractures of the femur.

Plaintiffs in this case are all Fosamax users who suffered atypical femoral fractures. They allege,

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[2] U.S. Dep't of Health & Human Servs., *Bone Health and Osteoporosis: A Report of the Surgeon General* 41 (2004).

[3] Pls. Br. 15 (citing A 884.)

among other things, that (1) Fosamax caused these atypical fractures by slowing the resorption process and allowing microcracks to accumulate. and (2) Merck was aware of the risk of such fractures but acted unlawfully by failing to warn doctors and patients of those dangers. They claim that Merck should have included a warning about atypical femoral fractures in the federally-mandated drug warnings that accompany prescription drugs. The interplay, and potential collision, between state-law warning duties and federal regulatory requirements is the subject of this appeal.

B. Regulatory Framework

The Food, Drug, and Cosmetic Act ("FDCA")[4] regulates the marketing and sale of prescription drugs in the United States. Under the FDCA, a manufacturer must obtain approval from the United States Food and Drug Administration ("FDA") before marketing a new drug.[5] As part of a new drug application, the manufacturer must submit a proposed package insert, commonly called the "drug label," that sets out the drug's medical uses ("indications") and health risks.[6] "To obtain FDA approval, drug companies generally must submit evidence from clinical trials and other testing that evaluate the drug's risks and benefits and demonstrate that it is safe and effective for all of the indications 'prescribed, recommended, or suggested'

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[4] 21 U.S.C. § 301 *et seq.*

[5] *Id.* § 355(a).

[6] 21 C.F.R. § 201.57(a); 21 U.S.C. § 355(b)(1)(F).

on the drug's label."[7] The FDA's approval of a new drug application is conditioned on its approval of the exact text of the drug label.[8]

Drug labels includes two sections relevant to this litigation: a "Warnings and Precautions" section and an "Adverse Reactions" section. The Warnings and Precautions section must describe "clinically significant adverse reactions," including any that are "serious even if infrequent."[9] The Adverse Reactions section requires a description of "the overall adverse reaction profile of the drug based on the entire safety database." including a list of all "undesirable effect[s]. reasonably associated with use of a drug."[10]

After a drug is approved, the FDA retains the authority to approve or require amendments to the drug's label.[11] The fundamental premise of the federal drug labeling scheme. however, is that "manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times."[12]

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[7] *In re Schering-Plough Corp. Intron/Temodar Consumer Class Action*, 678 F.3d 235, 239 (3d Cir. 2012) (quoting 21 U.S.C. § 355(d)).

[8] 21 C.F.R. § 314.105(b), (c).

[9] *Id.* § 201.57(c)(6)(i).

[10] *Id.* § 201.57(c)(7).

[11] 21 U.S.C. § 355(o)(4); 21; C.F.R. § 314.93; *see also Wyeth*, 555 U.S. at 567 (observing that the 2007 FDCA amendments "granted the FDA statutory authority to require a manufacturer to change its drug label based on safety information that becomes available after a drug's initial approval").

[12] *Wyeth*, 555 U.S. at 579; *see also* 21 U.S.C. § 355(o)(4)(I) ("Rule of construction" clarifying that the 2007 amendments to the

The manufacturer is charged not only "with crafting an adequate label" as an initial matter, but also "with ensuring that its warnings remain adequate as long as the drug is on the market."[13]

A manufacturer can fulfill its responsibility to revise the warnings on a drug label in two ways.

First, the "Changes Being Effected" ("CBE") regulation permits a manufacturer to unilaterally change a drug label to reflect "newly acquired information," subject to later FDA review and approval.[14] Under the CBE regulation, the manufacturer may, upon filing a supplemental application with the FDA, change a label to "add or strengthen a contraindication, warning, precaution, or adverse reaction"; it need not wait for FDA approval.[15] To add a warning to the Warnings and Precautions section through a CBE submission, "there need only be 'reasonable' evidence of a causal association with the drug, a standard that could be met by a wide range of evidence."[16] Thus, a

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FDCA "shall not be construed to affect the responsibility of the responsible person . . . to maintain its label in accordance with existing requirements").

[13] *Wyeth*, 555 U.S. at 571.

[14] 21 C.F.R. § 314.70(c)(6)(iii); *see also Wyeth*, 555 U.S. at 568 (discussing CBE amendment process).

[15] *Id.* § 314.70(c)(6)(iii)(A).

[16] 73 Fed. Reg. 49,603, 49,604 (Aug. 22, 2008) (FDA notice regarding final amendment to CBE regulation); *see also* 21 C.F.R. 201.57(c)(6)(iii) (Warnings and Precautions section "must be revised to include a warning about a clinically significant

manufacturer can amend the label to address potential adverse effects even if the evidence for a causal connection would "not also support a higher evidentiary standard, such as a finding that there is a 'preponderance' of evidence that a product actually causes a particular kind of adverse event."[17]

For purposes of the CBE regulation, "newly acquired information" includes "new analyses of previously submitted data."[18] This definition "accounts for the fact that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments."[19] Thus, if a manufacturer were to "determine[ ] that existing warnings were insufficient based on . . . a new analysis of previously submitted data, [it] could still submit a CBE based on its new analysis of the previous data."[20] A manufacturer's ability to change a label via the CBE process is not absolute, however. The FDA reviews CBE submissions and retains the power to reject proposed changes that do not meet the regulatory standards.[21]

Second, manufacturers can implement "major changes" to a label by filing a so-called "Prior

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hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.").

[17] 73 Fed. Reg. at 49,604.

[18] 21 C.F.R. § 314.3(b).

[19] *Wyeth*, 555 U.S. at 569.

[20] 73 Fed. Reg. at 49,606.

[21] *See* 21 C.F.R. § 314.70(c)(4)-(6).

Approval Supplement" ("PAS").[22] Unlike a CBE change, a PAS change requires prior FDA approval before it can be implemented.[23] The key distinction for present purposes is that a proposed label change that qualifies for a CBE supplement—including a proposal to "add or strengthen a contraindication, warning, precaution, or adverse reaction"— need not be submitted through the PAS process and does not require prior FDA approval.[24]

It is important to recognize, however, that the FDA does not simply approve warnings out of an abundance of caution whenever the manufacturer posits a theoretical association between drug use and an adverse event. As the FDA has recognized, "[e]xaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug."[25] Moreover, "labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance."[26] Accordingly, the FDA will reject a PAS application or CBE amendment if there is insufficient evidence of a causal link between drug use and the adverse event.[27]

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[22] *Id.* § 314.70(b).

[23] *Id.* § 314.70(b)(3).

[24] *Id.* § 314.70(b)(2)(v)(A); *id.* § 314.70(c)(6)(iii)(A) .

[25] 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008).

[26] *Id.*

[27] *Id.*

C. Fosamax Labeling History

Both Merck and the FDA have long been aware that anti-resorptive drugs like Fosamax could theoretically increase the risk of atypical femoral fractures. The question that both Merck and the FDA faced in the years following the drug's approval was whether the developing evidence of a causal link between Fosamax and atypical fractures was strong enough to require adding a warning to the Fosamax drug label. As explained further in Section II of this opinion, the primary question in this appeal is whether, prior to September 2010, the FDA would have rejected an attempt by Merck to unilaterally amend the Fosamax label (via a CBE submission) to include a warning about the risk of atypical femoral fractures. The following evidence bears on that question.

i. Early Studies Suggest a Possible Link Between Fosamax and Atypical Femoral Fractures

During Fosamax's development, Merck scientists and third-party researchers discussed the possibility that anti-resorptive drugs could inhibit a bone's ability to repair microdamage, potentially leading to stress fractures. In 1992, prior to FDA approval, Merck informed the FDA that "antiresorptive agents may inhibit microdamage repair by preventing . . . bone resorption at the sites of microdamage."[28] Nonetheless, when the FDA approved Fosamax in 1995 for the treatment of osteoporosis in postmenopausal women, it did not require Merck to

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[28] A 1774.

include a warning about bone fractures. Nor did it do so in 1997, when it approved Fosamax for the prevention of osteoporosis in postmenopausal women.

Between 1995 and 2010, scores of case studies, reports, and articles were published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures. Plaintiffs have directed our attention to six such studies from this period. None of these studies, however, concluded that Fosamax caused bone fractures, or even that Fosamax use was definitively associated with atypical fractures. Rather, they variously stated that Fosamax use "may . . . potentially" increase the risk of fracture[29] or "may be associated" with insufficiency fractures,[30] or that certain findings "raise[d] the possibility" that Fosamax use led to fractures.[31] Merck's assertion that the link between Fosamax and fracturing "remained hypothetical and unsubstantiated"[32] may be an understatement, but not even Plaintiffs suggest that there was definitive proof of a causal connection at this time.

Merck kept the FDA informed of these and other studies suggesting a possible association between bisphosphonates and fractures, either citing or submitting them in communications with the agency. In March 2008, Merck submitted a periodic safety

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[29] A 1258.

[30] A 1237.

[31] A 1243.

[32] Merck Br. 8.

update to the FDA that included over 30 pages of information regarding atypical femur fractures and suppression of bone turnover. Merck reported that "recent publications" had "implicated a link between prolonged bisphosphonate therapy and atypical low-energy non-vertebral fractures."[33] It also stated "the reporters related these findings to severely suppressed bone turnover that may develop during long-term" use of Fosamax.[34] Later that month, Merck forwarded to the FDA a letter published in the *New England Journal of Medicine* describing a "potential link between [bisphosphonate] use and low-energy fractures of the femur."[35]

In June 2008, the FDA informed Merck that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates."[36] It also stated that it was "concerned about this developing safety signal."[37] The FDA asked Merck to submit any investigations it had conducted or reports it had received regarding femoral fractures. Merck promptly complied.

ii. Merck Attempts to Amend the Fosamax Label

In September 2008, while the FDA was analyzing Merck's data, Merck submitted a PAS to the FDA. As discussed above, a PAS is a label-change request

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[33] A 2597.

[34] *Id.*

[35] A 1928-33.

[36] A 1935.

[37] *Id.*

that, unlike a CBE submission, requires prior approval from the FDA.[38] In the PAS, Merck proposed to add language to both the Warnings & Precautions and the Adverse Reactions sections of the label to address atypical femoral fractures. Merck explained that "[i]t is not possible with the present data to establish whether treatment with" Fosamax "increases the risk of [these] . . . low-energy subtrochanteric and/or proximal shaft fractures."[39] But because of the temporal association between these fractures and Fosamax use, Merck believed that it was "important to include an appropriate statement about them in the product label" to "increase physicians' awareness of possible fractures in some osteoporotic patients at risk and allow early intervention, thereby possibly preventing the progression to complete fracture and/or other complications."[40]

Merck proposed adding the following language to the Warnings and Precautions section of the label:

> **Low-Energy Femoral Shaft Fracture**
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area,

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[38] *See supra* Section I.B.

[39] A 1349.

[40] *Id.*

> often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.[41]

Merck also proposed adding "low-energy femoral shaft fracture" to the list of reported adverse reactions in the Adverse Reactions section of the label,[42] as well as the following statement to the Patient Package Insert: "Patients have experienced fracture in a specific part of the thigh bone. Call your doctor if you develop new or unusual pain in the hip or thigh."[43] In support of its PAS application, Merck included an analysis of femur fractures in Fosamax users and cited to nine articles reporting cases of low-energy femoral fractures in Fosamax users.

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[41] A 1371.

[42] A 1383.

[43] A 2742.

In April 2009, Merck representatives held a telephone conversation with Dr. Scott Monroe of the FDA. According to Merck's internal notes, Dr. Monroe stated that the FDA could agree to add language in the Adverse Reactions section of the label, but that Merck's "elevation of this issue to a precaution in the labeling" was prolonging review.[44] The FDA wanted "to approach the issue of a precaution from the [perspective] of all bisphosphonates" and was "working with the Office of Safety and Epidemiology to do so."[45] Dr. Monroe also stated that because "the conflicting nature of the literature does not provide a clear path forward, . . . more time will be need[ed] for FDA to formulate a formal opinion on the issue of a precaution around these data."[46]

Later in April 2009, an FDA liaison sent Merck an email stating that the FDA was not prepared to include language about low-energy femoral fractures in the Warnings and Precautions section of the label and would only approve a reference to atypical fractures in the "Adverse Reaction" section.[47] The FDA asked Merck to "hold off on the [Warnings and Precautions] language at this time" so that drug evaluators could "then work with [the FDA's Office of Surveillance and Epidemiology] and Merck to decide

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[44] A 1970-71.

[45] A 1971.

[46] 46 *Id.*

[47] A 1498.

on language for a [Warnings and Precautions] atypical fracture language. if it is warranted."[48]

In May 2009. the FDA sent Merck a "Complete Response" letter. authored by Dr. Monroe. In the Complete Response, the FDA approved the addition of "low energy femoral shaft and subtrochanteric fractures" to the Adverse Reactions section, but the FDA rejected Merck's proposed addition to the Warnings and Precautions section. Because the parties vigorously dispute the grounds for this rejection, it is worth excerpting the relevant portion of the FDA notice in full:

> We have completed the review of your [PAS] applications, as amended, and have determined that we cannot approve these applications in their present form. We have described below our reasons for this action and our recommendation to address this issue.
>
> 1. While the Division agrees that atypical and subtrochanteric fractures should be added to the **ADVERSE REACTIONS, Post-Marketing Experience** subsections of the [Fosamax] labels. your justification for the proposed **PRECAUTIONS** section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available

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[48] *Id.*

literature and post-marketing adverse event reporting.[49]

The outcome of this case hinges in large part on how one reads (or really, on how a reasonable jury could read) this language in conjunction with the FDA's accompanying actions and communications. Plaintiffs claim that the FDA was objecting only to Merck's use of the imprecise and potentially misleading term "stress fractures," and that the FDA would have approved a proposed warning that specifically discussed the risk of atypical femoral fractures while eliminating the general references to stress fractures. Merck claims that this letter, along with the FDA's other communications, demonstrates that the FDA simply did not believe there was sufficient evidence of a causal link between Fosamax use and atypical fractures, and would have rejected *any* proposed warning relating to such a risk.

iii. The FDA Revises its Position on the Link Between Bisphosphonates and Atypical Femur Fractures

In March 2010, after reviewing the data submitted by Merck and other manufacturers, the FDA stated publicly that the data reviewed to date had "not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures."[50] The FDA announced that it would work with an outside expert task force to gather additional information.

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[49] A 1500-01.

[50] A 1508.

In September 2010, the task force published a report finding that "there is evidence of a relationship between long-term [bisphosphonate] use and a specific type of subtrochanteric and femoral shaft fracture."[51] The report stated that although there was an association between longterm bisphosphonate use and atypical fractures, the association had not been proven to be causal. The FDA responded by issuing a Drug Safety Communication stating that, "[a]lthough it is not clear if bisphosphonates are the cause [of fractures], these unusual femur fractures have been identified in patients taking these drugs."[52] Regarding the task force's recommendation of a label change, the FDA stated that it "has assembled and is thoroughly reviewing all long term data available on the products, as well as all safety reports" and would be "considering label revisions."[53]

In October 2010, the FDA announced that it would require all bisphosphonate manufacturers to add information regarding the risk of atypical femoral fractures to the Warnings and Precautions section of the drug labels, based on the FDA's conclusion that "these atypical fractures may be related to long-term . . . bisphosphonate use."[54] It reiterated that it

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[51] A 1167.

[52] A 1512.

[53] *Id.*

[54] A 1118. The FDA also announced that it would require a new Limitations of Use statement in the Indications and Usage section of the labels to "describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis." *Id.*

was still "not clear if bisphosphonates are the cause," but noted that "these unusual femur fractures have been predominantly reported in patients taking bisphosphonates."[55] In a conference call accompanying the announcement, the FDA's Deputy Director of the Office of New Drugs stated that the task force report made the FDA "confident" that atypical femur fractures are "potentially more closely related to" long-term use of bisphosphonates "than [the FDA] previously had evidence for."[56]

The same day, the FDA wrote to Merck requesting that Merck add the following language to the Warnings and Precautions section of the Fosamax label:

> Atypical Subtrochanteric and Diaphyseal Femoral Fractures:
>
> Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.
>
> Atypical femur fractures most commonly occur with minimal or no impact to the affected

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[55] *Id.*

[56] 56 A 1396.

> area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.
>
> Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out a femur fracture. Subjects presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.[57]

Merck responded by proposing additional language that, according to Merck, was intended to make clear that doctors should attempt to rule out stress fractures. The proposal contained five specific references to "stress fractures." The FDA responded to this proposal by eliminating every instance of the phrase "stress fractures." In rejecting Merck's proposal, the FDA explained that "the term 'stress fracture' was considered and not accepted. The Division believes that for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical

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[57] A 1516-17.

femoral fractures associated with bisphosphonate use."[58] The FDA subsequently approved language nearly identical to its original October 2010 proposal. That language was added to the Fosamax label in January 2011 and has remained there since.

D. Procedural History

After the label change, patients who had taken Fosamax and suffered atypical femur fractures filed lawsuits against Merck throughout the country. In May 2011, the Judicial Panel on Multidistrict Litigation consolidated these cases for pre-trial administration in a multi-district litigation ("MDL") in the District of New Jersey.[59] Since then, the MDL has been assigned to three different district judges[60] and has swelled to over 1,000 cases, each involving a separate patient who allegedly suffered a femur fracture after taking Fosamax.

Although no two complaints in the MDL are identical, all of the actions "share questions of fact arising from similar allegations that use of Fosamax . . . caused femur fractures or similar bone injuries."[61] The individual Plaintiffs in this appeal all allege that they were injured before September 14, 2010, the date the outside expert task force published its report documenting an association between

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[58] A 1540.

[59] *In re: Fosamax (Alendronate Sodium) Prods. Liab. Litig. (No. II)*, 787 F. Supp. 2d 1355 (J.P.M.L. 2011) (hereinafter, "*Fosamax MDL Order*").

[60] The MDL is currently assigned to the Honorable Freda Wolfson.

[61] *Fosamax MDL Order*, 787 F. Supp. 2d at 1356.

bisphosphonate use and atypical femur fractures. According to Plaintiffs,[62] the complaints filed by this cohort generally include a state-law products liability claim for failure to warn, alleging that Fosamax was defective because Merck failed to warn Plaintiffs and their physicians about the risk of atypical femur fractures. Many complaints also claim that Fosamax was defectively designed because the risks of Fosamax exceeded the benefits, or because Fosamax was unreasonably dangerous or more dangerous than an ordinary consumer would expect. Many complaints also include claims for, among other causes of action, negligence, negligent misrepresentation, breach of express and implied warranties, unjust enrichment, punitive damages, and violations of state consumer fraud and deceptive trade practice statutes.[63]

Merck has argued since the inception of the MDL that Plaintiffs' state-law failure-to-warn claims are preempted by FDA regulations. The District Court decided to address preemption after developing a full record in a bellwether trial, the so-called *Glynn* trial. Typical of all plaintiffs in this MDL, the lead plaintiff in *Glynn* claimed that she suffered an atypical femur fracture that was proximately caused by Merck's failure to include adequate fracture warnings on the

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[62] This appeal involves over 500 related cases, and the parties have wisely chosen not to include each complaint in the record. We are therefore necessarily reliant on the parties for information regarding the nature, prevalence and commonality of the plaintiffs' claims.

[63] Although the complaints exclusively plead state-law causes of action, the actions are in federal court on diversity grounds.

Fosamax label.[64] Merck moved for judgment as a matter of law on preemption grounds before and during trial, but the District Court reserved judgment.[65] The jury returned a verdict for Merck on the merits, finding that Ms. Glynn failed to prove by a preponderance of the evidence that she experienced an atypical femur fracture.[66] Despite this verdict, the District Court announced that it would still decide whether the Glynns' claims were preempted.[67]

In June 2013, the District Court issued an opinion concluding that the Glynns' failure-to-warn claim was preempted by federal law. Applying the Supreme Court's decision in *Wyeth*, the court stated that state-law failure-to-warn claims are preempted when "there is 'clear evidence that the FDA would not have approved a change' to the prescription drug's label."[68] The District Court concluded that the Glynns' claim was preempted because the FDA's May 2009 denial of Merck's request to add language about atypical femur fractures to the Warnings and Precautions section of the label was "clear evidence that the FDA would not have approved a label

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[64] Although the *Glynn* plaintiffs brought multiple claims, the only one they actually tried to verdict was a failure-to-warn claim. *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig. (Glynn v. Merck Sharp & Dohme Corp.)*, 951 F. Supp. 2d 695, 700 & n.5 (D.N.J. 2013) (hereinafter, "*Glynn*").

[65] *Id.* at 700-701.

[66] *Id.* at 701.

[67] *Id.*

[68] *Glynn*, 951 F. Supp. 2d at 702 (quoting *Wyeth*, 555 U.S. at 571).

change to the Precautions section of the label prior to Ms. Glynn's injury."[69]

Shortly after the *Glynn* decision, Merck moved for an order to show cause why all the cases in the MDL alleging injuries prior to the release of the September 2010 task force report should not be dismissed on preemption grounds. Plaintiffs opposed the motion on the ground that resolving their claims through a show-cause procedure would violate their due process right to individual trials. In August 2013, the District Court issued an Order to Show Cause why the pre-September 2010 claims should not be dismissed on preemption grounds, and the parties submitted briefing. Although both sides disputed the propriety of the show-cause procedure and the substance of Merck's preemption arguments, the parties and the District Court all agreed that Federal Rule of Civil Procedure 56 "provides the exclusive mechanism by which the Court can resolve the dispositive issues presented by Merck's preemption defense before trial(s)."[70]

After briefing, the District Court granted summary judgment to Merck and ruled that all claims made by plaintiffs who were injured prior to September 14, 2010 were preempted under *Wyeth*. Specifically, the court ruled that: (1) Merck had met its initial burden

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[69] *Id.* at 703.

[70] *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, MDL No. 2243, Master Dkt. No. 08-08 (JAP)(LHG), 2014 WL 1266994, at *8 (D.N.J. Mar. 26, 2014) (hereinafter, "*Summary Judgment Order*"). The parties continue to agree that Rule 56 is the proper framework to apply, although they dispute how to apportion the parties' burdens of production and persuasion.

of demonstrating that there was no genuine issue of material fact as to preemption in *Glynn*, and that Plaintiffs therefore bore the burden of producing a genuine issue for trial; (2) Plaintiffs had failed to create a genuine issue as to preemption; (3) it was proper to use a show-cause proceeding to apply the *Glynn* preemption ruling to other MDL cases; (4) Plaintiffs' design-defect and other non-warning claims were also preempted because they sounded in failure to warn; and (5) Plaintiffs' alternate theories that Merck should have added information about fractures to the Adverse Reactions section of the label prior to 2009 and should have warned that Fosamax's long-term benefits were limited should be dismissed.

With respect to the failure-to-warn claims, the District Court reiterated its conclusion from *Glynn* that "the fact that the FDA never required [Merck] to submit new language or change the label demonstrates that the FDA did not think that the label should have been changed at that time."[71] This evidence "remain[ed] unchanged" and provided "clear evidence that the FDA *would have* rejected a stronger Precautions warning because the FDA *did* reject a stronger Precautions warning."[72] As to the non-failure-to-warn claims (including claims for design defect, negligence, fraud, breach of warranty, deceptive trade practice, and unjust enrichment), the District Court concluded that that these claims "are based entirely on the premise that Fosamax had

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[71] *Id.* at *16 (quoting *Glynn*, 951 F. Supp. 2d at 703-04) (alterations omitted).

[72] *Id.*

risks which should have been disclosed to consumers" and therefore "ultimately hinge[ ] on the adequacy of Fosamax's warning."[73] Because these claims "rise and fall with a claim for failure to warn," they too were preempted.[74] This appeal followed.[75]

II. LEGAL BACKGROUND

The primary issue in this case is whether Plaintiffs' state-law failure-to-warn claims are preempted by federal law under the Supreme Court's decision in *Wyeth*. This is not a straightforward determination. *Wyeth* says only that a claim is preempted when there is "clear evidence" that the FDA would not have approved a label change. This standard is cryptic and open-ended, and lower courts have struggled to make it readily administrable. This appeal, however, requires us to do so. To assess whether Merck is entitled to summary judgment on

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[73] *Id.* at *12, *14.

[74] *Id.* at *12, *14.

[75] This appeal involves only those Plaintiffs who alleged that they were injured before September 14, 2010. *See, e.g., id.* at *17 (granting summary judgment to Merck on "all claims made by the Plaintiffs . . . with injuries that occurred prior to September 14, 2010"). Plaintiffs inform us that there are "approximately 570 remaining cases in the MDL involving plaintiffs who were injured after September 14, 2010." Pls. Br. 8; *see also* A 2067-80. In June 2015, the District Court conditionally dismissed these remaining actions without prejudice, concluding that they "are based on the alleged inadequacy of the pre-2011 Fosamax label" and that our decision here would "determine whether the claims of the remaining Plaintiffs in this litigation . . . remain viable or not." A 2065. We express no view regarding the effect of today's ruling on the remaining plaintiffs' claims.

its affirmative preemption defense, we must answer two questions: What is "clear evidence"? And who should determine whether clear evidence exists?

For the following reasons, we conclude that (1) the term "clear evidence" refers solely to the applicable standard of proof, and (2) the ultimate question of whether the FDA would have rejected a label change is a question of fact for the jury rather than for the court. By describing the ultimate question as one of fact for the jury, we do not mean to suggest that summary judgment is categorically unavailable to a manufacturer asserting a preemption defense. When there is no genuine issue of material fact—that is, when no reasonable jury applying the clear-evidence standard of proof could conclude that the FDA would have approved a label change— the manufacturer will be entitled to judgment as a matter of law. We simply hold that, at the summary judgment stage, the court cannot decide for itself whether the FDA would have rejected a change, but must instead ask whether a reasonable jury could find that the FDA would have approved the change.

A. Federal Preemption Doctrine: Impossibility Preemption and the Supreme Court's Decision in *Wyeth v. Levine*

i. Impossibility Preemption

The Supremacy Clause establishes that federal law "shall be the supreme Law of the Land."[76] The Supremacy Clause, therefore, preempts "state laws

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[76] U.S. Const., Art. VI, cl. 2.

that 'interfere with, or are contrary to,' federal law."[77] There are several varieties of preemption; the one at issue here is called "conflict" or "impossibility" preemption. Impossibility preemption applies, and state law must give way, when "it is 'impossible for a private party to comply with both state and federal requirements.'"[78] "The question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it."[79]

In this case, Plaintiffs claim that state law obligated Merck to add a warning about atypical femur fractures to the Fosamax label. At issue is whether federal law—here, FDA regulations—prevented Merck from adding the type of warnings that Plaintiffs claim were required under state law. The Supreme Court confronted a similar question in *Wyeth*, and its opinion governs our analysis here.

ii. The *Wyeth* Decision

In *Wyeth*, the Supreme Court addressed whether and to what extent state-law failure-to-warn claims are preempted by the FDCA and federal drug-labeling regulations. The Court held that failure-to-warn claims against drug manufacturers generally are not preempted by FDA approval of the drug's warning label. But such a claim *is* preempted by federal law when there is "clear evidence" that the

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[77] *Hillsborough Cty., Florida v. Automated Med. Labs., Inc.*, 471 U.S. 707, 712 (1985) (quoting *Gibbons v. Ogden*, 22 U.S. 1, 211 (1824)).

[78] *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 618 (2011) (quoting *Freightliner Corp. v. Myrick*, 514 U.S. 280, 287 (1995)).

[79] *Id.* at 620.

FDA would not have approved the warning that a plaintiff claims was necessary.

The plaintiff in *Wyeth* developed gangrene when a physician's assistant injected her with the antinausea drug Phenergan. She brought a state-law failure-to-warn claim against *Wyeth*, the manufacturer of Phenergan, for failing to provide an adequate warning about the risks involved with various methods of administering the drug. A jury concluded that the plaintiff's injury was caused by *Wyeth*'s inadequate warning label. *Wyeth* argued on appeal that the state-law failure-to-warn claims were preempted because it was impossible to comply with both state-law warning duties and federal labeling obligations.[80]

The Supreme Court rejected *Wyeth*'s argument. It began by citing the "central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times."[81] Under this rule, a manufacturer "is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market."[82] Thus, when the risks of a particular drug use become apparent, the manufacturer has "a duty to provide a warning that adequately describe[s] that risk."[83]

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[80] *Wyeth*, 555 U.S. at 559-64.

[81] *Id.* at 570-71.

[82] *Id.* at 571.

[83] *Id.*

In response to Wyeth's contention that federal law made it impossible to add the warnings the plaintiff claimed were necessary, the Court observed that drug manufacturers are allowed to strengthen an FDA-approved warning label without FDA approval through the CBE process.[84] Wyeth therefore could not establish impossibility preemption because the CBE regulation "permitted [Wyeth] to provide . . . a warning [of the risk of gangrene] before receiving the FDA's approval."[85]

The Supreme Court cautioned, however, that the mere availability of a CBE label amendment would not always defeat a manufacturer's preemption defense, because the FDA "retains authority to reject labeling changes."[86] Thus, where there is "clear evidence that the FDA would not have approved a change" to the label, federal law preempts state-law claims premised on the manufacturer's failure to make that change.[87] Impossibility preemption applies in that instance because the manufacturer would be legally prevented by the FDA from taking the very action that state law ostensibly requires.[88]

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[84] *Id.* at 568.

[85] *Id.* at 571.

[86] *Id.*

[87] *Id.*

[88] If a manufacturer retains a warning that the FDA has rejected, the drug may be deemed "misbranded" in violation of federal law. *See* 21 U.S.C. § 352(a) (drug shall be considered misbranded "[i]f its labeling is false or misleading in any particular"); A 1501 (FDA letter rejecting Merck's PAS proposal to amend the Fosamax label and stating that "[t]hese products

The manufacturer in *Wyeth* could not take advantage of the clear-evidence exception because it had "offered no such evidence" that the FDA would have rejected the warning sought by the plaintiff.[89] But the Supreme Court made it clear that if a manufacturer does present "clear evidence" that the FDA would reject a plaintiff's proposed warning, it would have a complete preemption defense to any state-law failure-to-warn claims.

In this case, Merck claims that the FDA's 2009 rejection of its proposed label amendment is just such "clear evidence."

B. Defining "Clear Evidence"

Courts applying the *Wyeth* preemption rule confront an immediate question: what is "clear evidence that the FDA would not have approved a change"? The *Wyeth* Court did not define the "clear evidence" standard or explain how courts should apply it. The only guidance the Court offered was to call impossibility preemption a "demanding defense."[90] In the absence of explicit direction or a coherent doctrinal framework, lower courts have been understandably reluctant to articulate firm definitions of the standard or its requirements. For example, several of our sister circuits have decided preemption cases by simply treating the facts of

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may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with this change before approval of these supplemental applications").

[89] *Wyeth*, 555 U.S. at 571-72.

[90] *Id.* at 573.

Wyeth as a yardstick: if the evidence for FDA rejection in a given case is less compelling than the manufacturer's evidence in *Wyeth*, the thinking goes, then there is clear evidence that the FDA would not have approved a label change and the manufacturer's preemption defense fails.[91] Many district courts have adopted a similar, if more complex. approach of exhaustively surveying the post-*Wyeth* case law and then testing the facts of a particular case against prior decisions.[92] Both approaches produce valid outcomes in individual cases, but neither clarifies or builds out the doctrine. The result is an anomaly in our preemption jurisprudence: the number of cases applying the clear evidence standard continues to

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[91] *See Mason v. Smithkline Beecham Corp.*, 596 F.3d 387, 392-96 (7th Cir. 2010) (stating that *Wyeth* provides an "intellectual anchor" because "if the evidence here is less compelling than it was in [*Wyeth*], we will not find preemption," and holding that preemption was unwarranted because the manufacturer's evidence was not "any more compelling"): *Gaeta v. Perrigo Pharms. Co.*, 630 F.3d 1225, 1235-37 (9th Cir. 2011) (observing that "the only guidance this court has is that the evidence presented in [*Wyeth*] was insufficient to meet the clear evidence standard" and holding that preemption was unwarranted "[b]ecause the evidence presented by Perrigo in this case is no more compelling than the evidence considered and rejected by the Supreme Court in [*Wyeth*]" (abrogated on other grounds, *PLIVA*, 564 U.S. 604).

[92] *See, e.g., In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d 1108 (S.D. Cal. 2015); *Seufert v. Merck Sharp & Dohme Corp.*, No. 13-cv-2169 AJB (MDD), 2016 WL 3369512 (S.D. Cal. May 11, 2016).

grow, yet "the clear evidence standard remains undefined."[93]

Today, we hold that the Supreme Court intended to announce a standard of proof when it used the term "clear evidence" in *Wyeth*.

The *Wyeth* Court articulated the "clear evidence" exception as follows: "[A]bsent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for *Wyeth* to comply with both federal and state requirements."[94] This formula has three components: (1) a legal rule that defines the circumstances in which a manufacturer is absolved of state-law liability (it must be impossible for the manufacturer to comply with both federal and state requirements); (2) a factual showing that satisfies the legal rule (the FDA would not have approved the proposed label change); and (3) a standard of proof that specifies how convincing the factual showing must be (the manufacturer must show that the FDA would not have approved the proposed label change by "clear evidence"). The term "clear evidence" therefore does not refer directly to the *type* of facts that a manufacturer must show, or to the circumstances in which preemption will be appropriate. Rather, it specifies how *difficult* it will be for the manufacturer to convince the factfinder that the FDA would have rejected a proposed label change. The manufacturer must prove that the FDA

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[93] *In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d at 1119.

[94] 555 U.S. at 571.

would have rejected a warning not simply by a preponderance of the evidence, as in most civil cases, but by "clear evidence."

Our conclusion that the *Wyeth* Court intended the term "clear evidence" to denote a standard of proof is supported by the Supreme Court's prior usage of the term. For example, the Court has consistently held that a complainant alleging official government misconduct must present "clear evidence" of unlawful behavior.[95] "Clear evidence" in this context is understood to be a standard of proof, rather than a condition on the type of facts that must be proven.[96] Similar examples are found in the bankruptcy and patent settings.[97]

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[95] *See, e.g., United States v. Chemical Found., Inc.*, 272 U.S. 1, 14-15 (1926) ("The presumption of regularity supports the official acts of public officers, and, in the absence of clear evidence to the contrary, courts presume that they have properly discharged their official duties."); *United States v. Armstrong*, 517 U.S. 456, 465 (1996) (criminal defendant alleging racially discriminatory prosecution must present "clear evidence" that prosecutorial policy had discriminatory effect and purpose); *Reno v. American-Arab Anti-Discrimination Comm.*, 525 U.S. 471, 489 (1999) (selective prosecution claim requires "clear evidence" of unlawful action).

[96] *See Reno*, 525 U.S. at 489 (stating that clear evidence is "the standard for proving" a selective prosecution claim); *United States v. Jarrett*, 447 F.3d 520, 525 (7th Cir. 2006) (describing clear evidence as "[t]he standard of proof" for selective prosecution claims).

[97] *See Oriel v. Russell*, 278 U.S. 358, 362-63 (1929) (when a party seeks turnover in a bankruptcy proceeding, "[a] mere preponderance of evidence . . . is not enough" and the court deciding the motion "should therefore require clear evidence"); *Microsoft v. i4i Ltd. P'ship*, 564 U.S. 91, 97, 11314 (2011)

Nor must we look far to discern the meaning of "clear evidence," as Supreme Court usage confirms that the term is synonymous with "clear and convincing evidence."[98] The latter is a well-recognized intermediate standard of proof—more demanding than preponderance of the evidence, but less demanding than proof beyond a reasonable doubt. Black's Law Dictionary defines clear and convincing evidence as "evidence indicating that the thing to be proved is highly probable or reasonably certain."[99] We adopt that definition here. It is consistent with both settled understanding and *Wyeth*'s instruction that the clear-evidence test is a "demanding defense" meant to represent a longstanding "presumption against pre-emption."[100]

We therefore conclude that for a defendant to establish a preemption defense under *Wyeth*, the factfinder must conclude that it is highly probable that the FDA would not have approved a change to the drug's label.

(Federal Circuit's interpretation of Patent Act as requiring "clear evidence" of invalidity accurately stated the statutory standard of proof).

[98] *See Microsoft*, 564 U.S. at 97, 113-14 (equating Federal Circuit's "clear evidence" standard with "clear and convincing" standard); *Oriel*, 278 U.S. at 362-63 (equating "clear evidence" with "clear and convincing evidence"); *accord Ramsey v. United Mine Workers of Am.*, 401 U.S. 302, 307-09, 311 (1971) (interpreting statute requiring "clear proof" as requiring "clear and convincing evidence").

[99] Black's Law Dictionary 674 (10th ed. 2009).

[100] *Wyeth*, 555 U.S. at 571-73, 565 n.3.

C. Whether the FDA Would Have Rejected a Label Change is a Question of Fact for the Jury

Once "clear evidence" is understood as a standard of proof rather than a condition on the type of facts to be proven, the *Wyeth* test narrows to a single inquiry: would the FDA have approved the label change that Plaintiffs argue was required?

Oral argument in this case revealed a fundamental yet unexplored disagreement between the parties. Merck claimed that the *Wyeth* preemption test presents a pure question of law that must be decided by a court, not a jury. Plaintiffs argued that *Wyeth* preemption poses a mixed question of fact and law that may require jury factfinding in appropriate circumstances. The distinction is crucial in this case because it dictates the course of our summary judgment analysis. If the question of whether the FDA would have rejected Plaintiffs' proposed warning is a question of law for the court, then we may simply answer it ourselves; but if it is a question of fact for the jury, then we must instead attempt to anticipate the range of answers that could be given by reasonable jurors applying the clear evidence standard and then determine whether summary judgment is appropriate. Having reviewed the case law and the parties' supplemental briefing on the issue, we conclude that the question of whether the FDA would have rejected a proposed label change is a question of fact that must be answered by a jury.[101]

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[101] Our discussion of the allocation of decision-making authority, both here and elsewhere in this Opinion, applies in

The court's role at the summary judgment stage is therefore limited to determining whether there are genuine issues of material fact that preclude judgment as a matter of law.

i. Conflict Preemption Can Require Fact Determinations by a Jury

Merck makes two general, threshold arguments in favor of treating *Wyeth* preemption as a purely legal question to be answered by the court.

First, Merck notes that the vast majority of courts applying *Wyeth* have assumed, either explicitly or implicitly, that *Wyeth* preemption presents a question of law. This observation is only somewhat accurate and wholly unpersuasive.

Wyeth does not indicate whether the "clear evidence" test poses a legal or factual question. Nor is it possible to divine a clear answer from the Supreme Court's application of the test in *Wyeth* itself.[102] However, the Supreme Court did decide

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cases tried to a jury. In a bench trial, of course, judicial factfinding will be both appropriate and necessary.

[102] Had *Wyeth* come up on appeal from a grant of summary judgment, for example, the Court would have been forced to address whether the question of what the FDA would have done should be answered by a court or by a jury. But *Wyeth* was an appeal of a post-trial motion for judgment, following a full jury trial and post-verdict proceedings in which the trial court made explicit fact findings, based on the trial record, directed at the preemption issue. *Wyeth*, 555 U.S. at 561-63. The Supreme Court concluded on the basis of that complete record that there was "no . . . evidence" that the FDA would have rejected a warning. *Id.* at 572. The combination of (1) a complete fact record that (2) contained zero evidence to support preemption

that the evidence presented in *Wyeth* was not sufficient to pass the clear evidence test. Therefore, in light of the Court's definitive holding that the evidence in *Wyeth* did not pass muster, the many federal courts that have applied the *Wyeth* preemption test have simply compared the evidence presented in their cases to the evidence presented in *Wyeth*. For example, in *Mason v. Smithkline Beecham Corp.*, the Seventh Circuit walked through the record evidence and concluded that, "in light of the extensive showing required by [*Wyeth*]," the manufacturer "did not meet its burden of demonstrating by clear evidence that the FDA would have rejected a label change."[103] The Ninth Circuit took a similar approach in *Gaeta v. Perrigo Pharmaceuticals Co.*, and explicitly stated that since "the only guidance this court has is that the evidence presented in [*Wyeth*] was insufficient to meet the clear evidence standard," the manufacturer would not meet the clear evidence standard if the "evidence in this case [is] less compelling than [that] in [*Wyeth*]."[104] Many other circuits have followed this approach and have found no preemption because the

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eliminated the need for remand, and thereby obviated the need to explain which judicial actor should make preemption-related findings in the first instance. And since the complete record contained no evidence whatsoever indicating that the FDA would not have approved a label change, the Supreme Court had no reason to consider whether a jury could have reached a contrary conclusion.

[103] *Mason*, 596 F.3d at 393-96.

[104] *Gaeta*, 630 F.3d at 1235-36.

evidence in those cases fell short of the record in *Wyeth*.[105]

It is possible to characterize this approach as a tacit acknowledgment that the "clear evidence" test is a legal question to be answered directly by the court. *Mason*, for example, was an appeal of a grant of summary judgment, but the court did not engage in a Rule 56 disputed-facts analysis or consider whether a reasonable jury could reach a contrary conclusion. At the same time the court also did not explain why the *Wyeth* test should be resolved by the court in the first instance. We do not lightly discount the wisdom of our sister circuits and the district courts that have grappled with these issues. But there is a difference between rejecting another court's considered judgment, on the one hand, and taking up an issue that has not been thoroughly analyzed, on the other. Furthermore, the approach taken by our sister circuits would be entirely consistent with our decision that the "clear evidence" test is a fact question that is ultimately for a jury to decide. After all, by comparing the evidence presented in these cases with

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[105] *See, e.g.*, *Demahy v. Actavis, Inc.*, 593 F.3d 428, 446 (5th Cir. 2010) ("The record here contains nothing, let alone 'clear evidence,' that suggests the FDA would have rejected a labeling proposal from Actavis."); *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 610-11 (8th Cir. 2009) ("The record contains nothing, let alone 'clear evidence,' to suggest the FDA would have rejected a labeling proposal from any of them."); *but see Miller v. Smithkline Beecham Corp.*, 381 F. App'x 776 (10th Cir. 2010) (unpublished) (without any prior discussion, remanding "to give the [district] court the opportunity to make evidentiary findings and analyze the record in light of [*Wyeth's*] new 'clear evidence' standard").

the evidence presented in *Wyeth*, these circuits are in fact engaging in a summary judgment analysis, even if they do not name it.

Second, Merck asserts that conflict preemption *always* presents a pure question of law. To be sure, we have made numerous offhand statements that seem to support Merck's position.[106] And as Merck points out, several district courts relying on similar language have concluded, albeit without substantial analysis, that a manufacturer's entitlement to the *Wyeth* preemption defense is a question of law for the court rather than the jury.[107]

The "rule" Merck cites, however, is one of thumb rather than law. It is true that *most* preemption cases present purely legal questions—for example, whether Congress intended to preempt state law, how to interpret the scope of an express preemption provision, or whether two regulatory schemes are facially incompatible. But it is equally clear that preemption can be, and sometimes must be, a fact question for the jury.

The Supreme Court's opinion in *Boyle v. United Technologies Corp.*[108] illustrates the distinction. In

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[106] *See, e.g., In re Federal-Mogul Global Inc.*, 684 F.3d 355, 364 n.16 (3d Cir. 2012) ("The scope of preemption presents a pure question of law, which we review *de novo*."); *Horn v. Thoratec Corp.*, 376 F.3d 163, 166 (3d Cir. 2004) ("This Court also exercises plenary review over a district court's preemption determination, as it is a question of law.").

[107] *See Dobbs v. Wyeth Pharms.*, 797 F. Supp. 2d 1264, 1267 (W.D. Okla. 2011); *In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d at 1114.

[108] 487 U.S. 500 (1988).

Boyle, as in *Wyeth*, the Supreme Court defined the scope of conflict preemption in a particular setting and announced the factual showing that a defendant must make to prove the affirmative preemption defense. Specifically, the Court held that "[l]iability for design defects in military equipment cannot be imposed, pursuant to state law, when (1) the United States approved reasonably precise specifications; (2) the equipment conformed to those specifications; and (3) the supplier warned the United States about the dangers in the use of the equipment that were known to the supplier but not to the United States."[109] The Court clarified that "whether the facts establish the conditions for the defense is a question for the jury."[110] The proper question on summary judgment, therefore, was whether a "reasonable jury could, under the properly formulated defense, have found for the petitioner on the facts presented."[111] It would be error, the Court said, for a court to "assess[ ] on its own whether the defense had been established."[112]

While our court has not gone so far as to declare that any one species of preemption defense categorically requires jury factfinding, we have acknowledged that the availability of the defense can turn on questions of fact. In *MD Mall Associates, LLC v. CSX Transportation, Inc.*,[113] we determined

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[109] *Id.* at 512.

[110] *Id.* at 514.

[111] *Id.*

[112] *Id.*

[113] 715 F.3d 479 (3d Cir. 2013).

that the question of whether state-law storm water trespass claims conflicted with federal railroad-safety regulations had to be addressed "under the circumstances of this particular case."[114] We therefore held that whether the defendant railroad could reasonably comply with federal drainage requirements while also complying with Pennsylvania law regarding storm water trespass "is a question of fact."[115] Having so concluded, we remanded for further development of the factual record.

Boyle and *MD Mall* confirm that the availability of a conflict preemption defense is not automatically a question of law that must be kept from the jury. The question, therefore, is whether there are independent jurisprudential or practical reasons to conclude that *Wyeth* preemption, specifically, requires a legal or a factual determination.

ii. Whether the FDA Would Have Approved a Label Change is a Factual Question Appropriate for the Jury

There are no general, hard-and-fast rules that we can use to distinguish fact questions from legal ones.[116] The Supreme Court has candidly acknowledged that "the appropriate methodology for

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[114] *Id.* at 496 (alteration omitted) (quoting *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 373 (2000)).

[115] *Id.*

[116] *See Pullman-Standard v. Swint*, 456 U.S. 273, 288 (1982) (the Supreme Court has not devised a "rule or principle that will unerringly distinguish a factual finding from a legal conclusion").

distinguishing questions of fact from questions of law has been, to say the least, elusive."[117] In the absence of a governing principle, we look to the fact/law distinctions drawn by our court in similar cases, practical considerations regarding the allocation of decision-making authority between judge and jury, and the text of *Wyeth* itself. What we discern from these sources is that the question at the heart of the *Wyeth* test—would the FDA have approved the label change plaintiffs argue was required?—is little different from the type of fact questions that are routinely given to a jury.

At root, *Wyeth* requires the decisionmaker to use an existing fact record to predict the outcome of a hypothetical scenario. The question posed to the decisionmaker in this case is: based on the contemporaneous medical literature and the interactions between Merck and the FDA that actually *did* happen, what *would* have happened if Merck had proposed the warning plaintiffs say was required? We think this question is one of fact, for three reasons.

First, we have recognized that an assessment of the probability of a future event should generally be categorized as a finding of fact, even if that finding automatically generates a legal consequence. In *Kaplun v. Attorney General of the United States*,[118] we held that a determination of the probability of future torture was a fact question subject to clear-error review. In so doing, we observed in general

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[117] *Miller v. Fenton*, 474 U.S. 104, 113 (1985).

[118] 602 F.3d 260, 269 (3d Cir. 2010).

terms that "[a] present probability of a future event is something distinct from its legal effect that is made up of facts and actually exists but is not a tangible thing, or actual occurrence."[119] Even though the future event has not occurred, and even if the prediction as to that event's likelihood is dispositive of a legal issue, "the likelihood itself remains a factual finding that can be made *ex ante* the actual outcome."[120] The *Kaplun* panel cited a number of other nonimmigration cases in which we or other circuits have held that inferences drawn from historical facts concerning the likelihood of future events are findings of fact, not law.[121] Here, the corresponding conclusion is that the task of assessing the probability that the FDA would have rejected a particular warning is a factual inquiry rather than a legal one.[122]

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[119] *Id.* at 269 (alterations and internal quotations omitted).

[120] *Id.* at 269-70. In other words, the likelihood of an event occurring "is what a decision-maker in an adjudicatory system decides now as part of a factual framework for determining legal effect." *Id.* at 269.

[121] *See United States v. Stewart*, 452 F.3d 266, 273 (3d Cir. 2006) (whether the release of an individual creates a substantial risk of future danger to society is a finding of fact); *Martin v. Cooper Elec. Supply Co.*, 940 F.2d 896, 900 (3d Cir. 1991) (inferences from historical facts are factual findings reviewed for clear error); *Onishea v. Hopper*, 171 F.3d 1289, 1300-01 (11th Cir. 1999) (en banc) (district court's finding as to the risk of future prison violence based on conflicting evidence was a factual determination reviewed for clear error).

[122] We recognize that the *Wyeth* test is something of an oddity. In a typical case, the historical facts are in dispute and the jury is tasked with figuring out what actually happened. In the case

Second, *Wyeth* requires the decisionmaker to weigh conflicting evidence and draw inferences from the facts—tasks that the Supreme Court tells us "are jury functions, not those of a judge."[123]

The present case is illustrative. Plaintiffs, for their part, rely heavily on the May 2009 letter from Dr. Scott Monroe of the FDA rejecting Merck's proposed warning. According to Plaintiffs, the text of this letter demonstrates that the FDA (or at least Dr. Monroe) objected only to the allegedly misleading term "stress fractures," and does not establish that the FDA was unconvinced of the link between bisphosphonate use and atypical femur fractures. Merck, meanwhile, directs our attention away from Dr. Monroe's letter and instead toward a series of informal FDA communications from the same time period between Dr. Monroe and Merck, which they claim demonstrate that the FDA (or at least Dr. Monroe) was unconvinced of a scientifically-proven link between bisphosphonates and atypical fractures.[124] In short: both sides ask us to (1) draw competing inferences from separate pieces of record

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before us, the historical facts are largely undisputed, and the primary disputed fact is the ultimate fact of what *would* have happened. This fact is in turn wholly determinative of the legal question. The law is clear, however, that "an issue does not lose its factual character merely because its resolution is dispositive of the ultimate constitutional question." *Miller*, 474 U.S. at 113. That is the same basic conclusion we reached in *Kaplun*: just because a fact finding completely resolves a legal issue does not alter its fundamentally "factual" character.

[123] *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986).

[124] *See* A 1498, 1971.

evidence and (2) weigh those inferences against one another. These are tasks reserved for jurors, not judges.

Third, the task of predicting the FDA's likely actions requires multiple assessments of FDA officials' motives and thought processes. Consider, for example, some of the questions that must be answered to arrive at a determination of whether the FDA would have rejected Plaintiffs' warning. How convinced or skeptical were FDA officials of the link between bisphosphonates and atypical femur fractures? Even if FDA officials were unconvinced of a firm link, might they nonetheless have agreed that there was "reasonable evidence of a causal association," as the CBE regulation requires? Did the FDA reject Merck's 2009 proposal because it was unconvinced by the science or because it disliked the stress-fracture language? What, if anything, can we infer from Dr. Monroe's contemporaneous oral statement that the "conflicting nature of the literature" concerning a possible fracture link "does not provide a clear path forward"? Whatever the FDA's position might have been on the association between bisphosphonates and atypical femur fractures, was that position an accurate predictor of its likely response to a proposed warning? In other words, how confidently can we extrapolate FDA officials' hypothetical reactions from their previous statements and actions?

These are all, essentially, inquiries about motive or state of mind: what were FDA officials thinking, and how would that disposition have conditioned their response to plaintiffs' hypothetical proposed warning? And questions of motive, intent, and state

of mind are typically understood to be fact questions committed to the jury rather than the court.[125]

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[125] *See Pullman-Standard*, 456 U.S. at 288 ("Treating issues of intent as factual matters for the trier of fact is commonplace."); *Monteiro v. City of Elizabeth*, 436 F.3d 397, 405 (3d Cir. 2006) ("Motive is a question of fact that must be decided by the jury"); *Grant v. City of Pittsburgh*, 98 F.3d 116, 125 (3d Cir. 1996) ("[T]he issue of state of mind will always be a question of fact").

One might object that the FDA acts as a body rather than through individuals, thereby rendering questions of "motive" and "intent" irrelevant in this setting. The key evidence in this case belies that assumption. At oral argument, Merck's counsel stated that the single best piece of evidence that the FDA would have rejected a revised warning is a set of notes, prepared by a Merck employee, recounting a telephone conversation with Dr. Monroe of the FDA—the same official who wrote the May 2009 letter formally rejecting Merck's proposed additions to the Warnings and Precautions section. According to the employee's notes, Dr. Monroe said that Merck's "elevation of this issue to a precaution in the labeling" was prolonging review, that the "FDA would like to approach the issue of a precaution from the [perspective] of all bisphosphonates," and that because the "conflicting nature of the literature does not provide a clear path forward, . . . more time [would] be need[ed] for [the] FDA to formulate a formal opinion on the issue of a precaution around these data." A 1971.

To gauge the import of these statements, a decisionmaker would need to, at a minimum, (1) make a credibility determination regarding the Merck employee who drafted the notes; (2) determine the veracity and accuracy of the notes; (3) determine the semantic meaning of Dr. Monroe's statements; (4) infer Dr. Monroe's intent and state of mind when making the statements; and (5) weigh that inference against whatever competing inferences can be drawn from Dr. Monroe's subsequent letter rejecting Merck's proposed warning. These are precisely the types of personal evaluations and weight-of-the-evidence assessments that we commit to jurors in the first instance.

As a fallback position, Merck argues that even if the *Wyeth* inquiry is factual in nature, it should be committed to the court rather than the jury for reasons of institutional competence.[126] Merck relies heavily on *Markman v. Westview Instruments, Inc.*,[127] in which the Supreme Court held that "construction of a patent, including terms of art within its claim, is exclusively within the province of the court."[128] The *Markman* Court based this conclusion, in part, on the general rule that "[t]he construction of written instruments is one of those things that judges often do and are likely to do better than jurors."[129] Here, the question of how the FDA would have responded to a proposed warning is informed by the regulations

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We acknowledge, of course, that the *Wyeth* inquiry may sometimes require the factfinder to impute motive or intent to the FDA as a whole. But as the Supreme Court has recognized, the difficulty of assessing collective intent is not a reason to treat the assessment as something other than a factual inquiry. For example, the Court has held that the question of whether a corporation harbored discriminatory intent is a question of fact. *Pullman-Standard*, 456 U.S. at 289 ("[D]iscriminatory intent . . . is not a question of law and not a mixed question of law and fact."). Here too, the questions of why the FDA took certain actions or what can be inferred from its pronouncements are questions of fact for a jury.

[126] *See Miller*, 474 U.S. at 114 ("[T]he fact/law distinction at times has turned on a determination that, as a matter of the sound administration of justice, one judicial actor is better positioned than another to decide the issue in question.").

[127] 517 U.S. 370 (1996).

[128] *Id.* at 372.

[129] *Id.* at 388.

that constrain FDA action—in this case, the CBE regulation. That regulation permits the FDA to add an adverse reaction in the Warnings and Precautions section "as soon as there is reasonable evidence of a causal association with a drug."[130] Agency guidance clarifies that "reasonable evidence" is "a standard that could be met by a wide range of evidence," including evidence that "would not also support a higher evidentiary standard, such as a finding that there is a 'preponderance' of evidence that a product actually causes a particular kind of adverse event."[131] Merck therefore claims that application of the clear evidence standard should be left to the courts because it "calls for the interpretation of regulations and agency records freighted with legal meaning."[132]

This argument misapprehends the nature of the factfinder's task under *Wyeth*. That task is to predict how the FDA would have reacted in a hypothetical scenario. The jury therefore is not being asked to supply a plenary construction of the CBE regulation (or any other written instrument) in the first instance. It is instead being asked to *apply* the requirements of that regulation to the facts, in aid of a prediction as to the FDA's behavior.

The operative language in the CBE regulation is neither uncommon nor abstruse. The "reasonable evidence of a causal association" standard requires law-to-fact applications of the sort that courts routinely give to juries in tort cases. It combines two

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[130] 21 C.F.R. § 201.57(c)(6)(i).

[131] 73 Fed. Reg. 49,603, 49,604 (Aug. 22, 2008).

[132] Merck Supp. Ltr. Br. 4.

classic jury questions: (1) whether a causal link between two events is too attenuated, and (2) whether the evidence meets a certain proof threshold. These determinations are well within the province of a properly instructed jury, and we do not think that their inclusion in the larger *Wyeth* inquiry merits reallocation of the factfinding function.

Plaintiffs, meanwhile, argue that judicial decision-making is required when a preemption determination "depends on construction of final, written regulatory actions by the FDA."[133] They further claim that the FDA's May 2009 response letter is just such a "final" document, and urge us to construe it "as a matter of law."[134] We will not go so far. As noted above, it is true that courts are typically charged with determining the construction (*i.e.*, the legal effect) of a writing, as opposed to its interpretation (*i.e.*, the semantic meaning of specific terms). But that general rule has little bearing on the disposition of this case. The question for preemption purposes is whether the FDA would have approved a different label amendment than the one it actually rejected in the May 2009 letter. The factfinder therefore must parse the FDA's May 2009 letter not to determine its legal effect in the first instance, but rather to discern what it suggests about the FDA's likely response to a differently worded proposal. This too is an appropriate task for the jury.[135]

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[133] Pls. Supp. Ltr. Br. 3.

[134] *Id.* 4.

[135] We do not opine on Plaintiffs' contention that the May 2009 letter rejecting Merck's PAS application was a "final regulatory

action." If in future cases a court is confronted with a formal regulatory pronouncement that has the force or effect of law, it may be necessary for the court to determine the scope of its legal effect before submitting the ultimate fact question to the jury. A request for such a ruling could be made by motion in limine or at summary judgment. But that exercise is unnecessary here because the immediate "legal" effect of the May 2009 letter, if any, was simply to reject Merck's proposed warning. That limited determination informs but does not answer the larger question of whether the FDA would have approved a differently-worded warning.

Pivoting to the merits, Plaintiffs direct our attention to an FDA regulation stating that an FDA response letter must "describe all of the specific deficiencies that the agency has identified" in an application. 21 C.F.R. § 314.110(a). Plaintiffs claim that since the May 2009 FDA response letter did not mention any concern over the scientific evidence of a causal association between Fosamax and fractures, we can determine as a matter of law that the FDA would have accepted a proposal that eliminated reference to stress fractures. This is a step too far. Again, the question for the factfinder is whether the FDA would have approved a different warning from the one it rejected. The combination of § 314.110's "complete description" requirement and the FDA's silence in the May 2009 response letter could certainly permit an inference about the FDA's contemporaneous thinking, and thereby an additional inference about how the FDA would have responded to a different warning. But it does not, and cannot, prove *as a matter of law* that the FDA would have accepted a warning of the type proposed by Plaintiffs.

Nor, for that matter, are we ready to blindly accept Plaintiffs' implicit assumption that Dr. Monroe, the author of the May 2009 letter, followed § 314.110 to a T or had its requirements foremost in mind when drafting. After all, Merck's contention is that Dr. Monroe gave additional reasons for the rejection, not disclosed in the May 2009 letter, in his telephone communications with Merck. We of course do not mean to impugn Dr. Monroe or to suggest that the May 2009 letter did not in fact comply with § 314.110. But the facts of this case

Accordingly, we do not see any convincing prudential reasons to commit the *Wyeth* inquiry to a court rather than a jury. The basic question that *Wyeth* poses to a factfinder—in a counterfactual setting, what do you think the FDA would have done?—requires an evaluative inference about human behavior based on correspondence, agency statements, contemporaneous medical literature, the requirements of the CBE regulation, and whatever intuitions the factfinder may have about administrative inertia and agency decision-making processes. This assessment is certainly complex, but it does not require any special legal competence or training.

We therefore conclude that the question of whether the FDA would have approved a plaintiff's proposed warning is a question of fact for the jury. A state-law failure-to-warn claim will only be preempted if a jury concludes it is highly probable that the FDA would not have approved a label change.

This decision would change how the preemption defense is presented and utilized in only a subset of cases. As before, drug manufacturers are free to raise a preemption defense, and either party may move for summary judgment on this issue after discovery. Upon summary judgment, district courts will compare the evidence presented with the evidence in *Wyeth*, to determine whether it is more or less compelling. This is in effect what the other

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demonstrate that we cannot presume the existence of undisputed facts based solely on anticipated compliance with a regulatory rule.

circuits have done. A trial by jury would only be necessary in those cases where the evidence presented is more compelling than that in *Wyeth* but no "smoking gun" rejection letter from the FDA is available. And this need not be at a great expense to either the litigants or the taxpayers. A combined trial may be conducted on both the liability and the defense—similar to patent infringement cases where the plaintiffs present their infringement case at the same time as the defendants present their patent invalidity defense—particularly because the evidence presented will likely overlap. In sum, today's holding will not drastically change how defendants will litigate the preemption defense.

III. ANALYSIS

Having clarified the "clear evidence" standard, we now turn to the merits of Merck's preemption defense.[136]

Plaintiffs' causes of action fall into three groups. The first group comprises Plaintiffs' claims that Merck failed to warn Fosamax users of the risk of atypical femur fractures by failing to add a warning to the Warnings and Precautions section of the label before September 2010 (the "Warnings and Precautions Claims"). The second group comprises Plaintiffs' claims that Merck failed to warn Fosamax users of the risk of femur fractures by failing to add atypical femur fractures to the Adverse Reactions section of the label prior to May 2009 (the "Adverse Reactions Claims"). The third group comprises all of

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[136] The District Court had subject matter jurisdiction under 28 U.S.C. § 1332. We have jurisdiction under 28 U.S.C. § 1291.

Plaintiffs' non-failure-to-warn claims, including design defect, negligence, breach of implied and express warranties, and violations of state consumer fraud and trade practice statutes (the "Non-Warning Claims"). The District Court ruled that the Warnings and Precautions claims were preempted under *Wyeth*; that the Adverse Reactions claims failed on the merits; and that the Non-Warning Claims were functionally indistinguishable from the Warnings and Precautions Claims and therefore preempted to the same extent.

Plaintiffs present four arguments on appeal. ***First***, Plaintiffs argue that the Warnings and Precautions Claims are not preempted as a matter of law because a reasonable jury could conclude that the FDA would have approved a properly worded atypical-fractures warning. ***Second***, Plaintiffs argue that Merck is not entitled to summary judgment on Plaintiffs' Adverse Reactions Claims because those claims were properly pleaded and there is sufficient evidence for a reasonable jury to find for the Plaintiffs. ***Third***, Plaintiffs argue that even if both sets of failure-to-warn claims are preempted, Plaintiffs' remaining claims are not preempted because they do not "sound in failure to warn" and are supported by competent evidence. ***Fourth***, Plaintiffs claim that the District Court misapplied Rule 56 when it tried to resolve Merck's affirmative preemption defense via a show-cause proceeding.

For the reasons set forth below, we conclude that (1) the Warnings and Precautions claims are not preempted as a matter of law because a reasonable jury could find it less than highly probable that the FDA would have rejected Plaintiffs' proposed

warning; (2) Merck is not entitled to summary judgment on the Adverse Reactions claims; and (3) the Non-Warning Claims are not preempted as a matter of law. Because we are vacating the District Court's summary judgment order, we do not reach the propriety of the show-cause order.

A. Summary Judgment Standard

Our review of a District Court's grant of summary judgment is plenary,[137] and we affirm only if "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law."[138] Because Merck moved for summary judgment, we must draw all reasonable inferences in the Plaintiffs' favor when considering the evidence.[139] Our inquiry is confined to "whether the evidence of record is such that a reasonable jury could return a verdict for the nonmoving party."[140] We therefore cannot grant summary judgment in Merck's favor "unless a reasonable juror would be compelled to find its way on the facts needed to rule in its favor on the law."[141]

Special considerations arise in the preemption context. Impossibility preemption is an affirmative defense[142] on which Merck bears the burdens of

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[137] *Reedy v. Evanson*, 615 F.3d 197, 210 (3d Cir. 2010).

[138] Fed. R. Civ. P. 56(a).

[139] *Anderson*, 477 U.S. at 255.

[140] *Reedy*, 615 F.3d at 210.

[141] *El v. Se. Pa. Transp. Auth.*, 479 F.3d 232, 238 (3d Cir. 2007).

[142] *PLIVA*, 564 U.S. at 634.

production and persuasion.[143] Crucially, "the inquiry involved in a ruling on a motion for summary judgment . . .necessarily implicates the substantive evidentiary standard of proof that would apply at the trial on the merits."[144] As discussed above, *Wyeth*'s "clear evidence" standard of proof requires the manufacturer to prove that it is *highly probable* that the FDA would not have approved a change to the drug's label. Therefore, the question for summary judgment purposes is not just whether a reasonable juror could find that the FDA would have approved Plaintiffs' proposed warning. It is whether a reasonable juror could find that it is highly probable that the FDA would have rejected the warning. Put differently: even if it seems possible or plausible that the FDA would have rejected the proposed warning, could a reasonable juror nonetheless conclude that the odds of rejection were something less than highly probable? In *El v. Southeastern Pennsylvania Transportation Authority*, we said that "if there is a chance that a reasonable factfinder would not accept a moving party's necessary propositions of fact, pre-trial judgment cannot be granted."[145] The corresponding proposition here is: if there is a chance that a reasonable factfinder would not find that it is highly probable that the FDA would have rejected Plaintiffs' warning, pre-trial judgment cannot be granted.

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[143] *El*, 479 F.3d at 237 & n.6.

[144] *Anderson*, 477 U.S. at 252.

[145] *El*, 479 F.3d at 238.

In summary: to affirm the District Court's decision that the Warnings and Precautions Claims are preempted, we must find that no reasonable juror could conclude that it is anything less than highly probable that the FDA would have rejected Plaintiff's proposed atypical-fracture warning had Merck proposed it to the FDA in September 2010.

B. Merck is Not Entitled to Summary Judgment on Plaintiffs' Warnings and Precautions Claims

Merck's ultimate task under *Wyeth* is to prove by clear evidence that the FDA would not have approved the warning about the link between Fosamax use and atypical femur fractures that Plaintiffs say was required under state law. Merck's primary argument on appeal is that prior to September 2010, the FDA would have opposed *any* warning about atypical femur fractures in the Warnings and Precautions section because the FDA did not believe that the science supported such a warning. As Merck points out, the FDA sought and analyzed information regarding atypical femur fractures in 2008; Merck responded with data and then proposed warning language for both the Warnings and Precautions and Adverse Reactions sections of the Fosamax label; the FDA rejected Merck's proposed language for the Warnings and Precautions section; and in correspondence surrounding the rejection, FDA officials stated that the "conflicting nature of the literature does not provide a clear path forward," and "more time [would] be need[ed] for [the] FDA to formulate a formal opinion on the issue of a

precaution around these data."[146] Given this sequence of events, Merck argues that there is clear evidence that the FDA would not have approved a CBE submission adding an atypical-fracture warning to the Warnings and Precautions section.

It is undisputed that the FDA was aware of the possible link between Fosamax and atypical fractures well before September 2010. In March 2008, Merck submitted a comprehensive safety update to the FDA reporting the existence and results of numerous studies suggesting just such an association. The FDA responded that it was concerned about this "safety signal," but did not require Merck to update its label.[147] In March 2010, after reviewing the data submitted by Merck and other manufacturers, the FDA stated that the data reviewed to date had "not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures."[148] And in October 2010, an FDA Deputy Director stated that the September 2010 task force report was the finding that for the first time made the FDA "confident" that atypical femur fractures are "potentially more closely related to" bisphosphonates "than [the FDA] previously had evidence for."[149] Merck argues that this evidence demonstrates that prior to September 2010, the FDA would have rejected *any* CBE application that attempted to add an atypical fractures warning to the Fosamax label

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[146] A 1971; *see also* A 1498.

[147] A 1935-36.

[148] A 1508.

[149] A 1396.

because the FDA had concluded that there was no reasonable evidence of a causal link.

Merck also emphasizes the FDA's April 2009 e-mail asking Merck to "hold off on the [Warnings and Precautions] language at this time" so that drug evaluators could "work with [the FDA's Office of Surveillance and Epidemiology] and Merck to decide on language for a [Warnings and Precautions] atypical fracture language, *if it is warranted.*"[150] After the task force issued its report in September 2010, by contrast, the FDA revised Merck's proposed language and quickly approved a label amendment. Merck argues that the "only logical conclusion from this course of proceedings is that the FDA thought adequate scientific support showing a connection between bisphosphonates and atypical femur fractures was lacking in 2009 but present in 2010 after the [task force] report, all of which accords with the FDA's public statements on the issue."[151]

Merck also rejects Plaintiffs' theory that the FDA rejected Merck's proposed warning based on a "language quibble" about stress fractures rather than a fundamental disagreement about the science. Merck's strongest argument for summary judgment is that Plaintiffs' theory of the case rests on an unreasonable inference: that the FDA (1) recognized a need to include risk information about atypical femur fractures and therefore would have accepted a properly-worded warning about such fractures, but (2) was so troubled by the "stress fracture" language

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[150] A 1498 (emphasis added).

[151] Merck Br. 50.

that it "preferred to deprive physicians of that risk information rather than allow Merck to add its proposed language or authorize inclusion of revised language."[152] Merck buttresses this argument by pointing to statutory language requiring the FDA to notify a drug manufacturer when it "becomes aware of new safety information that [it] believes should be included in the labeling of the drug" and to "initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information" if it is dissatisfied with the manufacturer's response.[153] Merck points out that if the FDA actually thought that an atypical-fracture warning was warranted, it could have proposed revisions rather than simply rejecting Merck's proposal. The FDA engaged in just such a revision process in 2010 after it directed Merck to add a warning and Merck responded by adding stress-fracture language. The fact that the FDA did not similarly reach out in 2009, Merck says, demonstrates that it would not have accepted Plaintiffs' proposed warning prior to the issuance of the task force report in September 2010.

We do not discount the force of this evidence or its potential to sway a jury. The problem for Merck, however, is that we are not assessing in the first instance whether there was clear evidence that the FDA would have rejected a change. We are instead trying to anticipate whether a reasonable juror, looking at all the evidence and trying to reconstruct a

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[152] *Id.* 48.

[153] 21 U.S.C. §§ 355(o)(4)(A) and (C).

hypothetical event, could conclude that it is less than highly probable that the FDA would have rejected the change. And crucially for the Plaintiffs, we are drawing all reasonable inferences in their favor. This confers a unique advantage when the factfinder's task is to guess what could have happened in a counterfactual setting.

Plaintiffs' argument against preemption centers on two claims: first, that there was sufficient evidence of a causal link to allow Merck to unilaterally amend the Fosamax label via the CBE process; and second, that the FDA's rejection of Merck's PAS application was based on Merck's misleading use of the term "stress fractures" rather than any fundamental disagreement with the underlying science. In our view, a reasonable jury could accept both contentions and conclude that the FDA would not have rejected Plaintiffs' proposed warning—or, at least, that the FDA was not highly probable to do so.

First, a reasonable jury could conclude that Merck could have amended the Fosamax label via the CBE process. To add a warning to the Warnings and Precautions section of a drug label through a CBE submission, "there need only be 'reasonable' evidence of a causal association with the drug, a standard that could be met by a wide range of evidence."[154] To gain FDA approval, therefore, the agency does not need to be affirmatively *convinced of* a causal link between the drug and the adverse event. Here, there is

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[154] 73 Fed. Reg. at 49,604. The same "reasonable evidence" standard that governs whether a manufacturer can submit a CBE application also governs whether the FDA should approve it. 21 C.F.R. § 201.57(c)(6)(i).

evidence that the FDA recognized a fracture risk and the possible need for warnings before September 2010. In June 2008, for example, the FDA stated that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates," that these and atypical femoral fractures were "reportedly rare in patients with osteoporosis not on bisphosphonates," and that it was "concerned about this developing safety signal."[155] And in May 2009, the FDA approved Merck's request to add a reference to "low energy femoral shaft and subtrochanteric fractures" in the Adverse Reactions section of the label.[156] Even if the FDA did not perceive a "clear connection" between Fosamax and atypical fractures, as it said in early 2010, a juror could conclude that the FDA would still have determined that "reasonable evidence" of a link existed—or more precisely, that the possibility of rejection was less than highly probable.

Second, a reasonable jury could also conclude that the FDA rejected Merck's proposed warning about femoral fractures in 2009 not because it denied the

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[155] A 1145.

[156] A 1500-01. As Plaintiffs point out, warnings can only be added to the Adverse Reactions section if they are "reasonably associated with use of" a drug and "there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event." 21 C.F.R. § 201.57(c)(7) (FDA regulation describing requirements of "Adverse Reactions" section of label). A juror could therefore infer from the FDA's approval of the Adverse Reactions language that the FDA would have also agreed that there was "reasonable evidence of a causal association" between Fosamax and atypical femoral fractures.

existence of a causal link between Fosamax and fractures, but because Merck repeatedly characterized the fractures at issue as "stress fractures." Merck's proposed warning used the phrase "stress fractures" six times.[157] According to Plaintiffs' expert, stress fractures are commonly seen in physically active people; atypical femoral fractures

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[157] The following is the text of Merck's proposed addition to the Warnings and Precautions section, with references to "stress fractures" bolded:

> Low-Energy Femoral Shaft Fracture
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. **Some were stress fractures** (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, **often associated with imaging features of stress fracture**, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and **stress fractures with similar clinical features also have occurred** in patients not treated with bisphosphonates. **Patients with suspected stress fractures** should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment. A 2720.

are, as the name suggests, highly unusual.[158] Stress fractures are usually incomplete fractures that heal with rest, while atypical femoral fractures often are complete fractures that require surgical intervention.[159] The FDA's response to Merck's PAS application stated: "Your justification for the proposed PRECAUTIONS section language is inadequate. Identification of 'stress fractures' may not be clearly related to the atypical subtrochanteric features that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting."[160] The FDA did not give any other reason for rejecting Merck's proposed warning.

In 2010, when Merck attempted to revise the FDA's proposed warning by adding references to stress fractures, the FDA again struck out the stress-fracture references. It explained that "the term 'stress fracture' was considered and was not accepted" because "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use."[161]

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[158] A 868 ¶ 22; A 881 ¶ 74; A 882 ¶ 76; *see also* A 1147 (task force report describing atypical femoral fractures as occurring with "relative rarity").

[159] A 884 ¶ 83-84; *see also* A 1149 (task force report describing atypical femoral fractures as "[c]omplete fractures").

[160] A 1500-01.

[161] A1540.

As discussed above, Merck argues that if the FDA had been truly concerned about the risk of atypical fractures, it could have revised and approved a warning without the offending stress-fracture references. As a matter of law, however, the burden and the responsibility to correct a drug label rests with the manufacturer, not the FDA.[162] Once the FDA rejected Merck's proposal, the ball was back in Merck's court to submit a revised, corrected proposal. A reasonable juror could therefore conclude that it was Merck's failure to re-submit a revised CBE or PAS without stress-fracture language, rather than the FDA's supposedly intransigent stance on the science, that prevented the FDA from approving a label change.

Plaintiffs' evidence certainly does not *compel* the conclusion that the FDA would have accepted an atypical fracture warning that omitted the language about stress fractures. But our inquiry at this stage is not about who has the best evidence; it is about what a reasonable jury applying a heightened standard of proof *could* conclude on the basis of the evidence. Because the *Wyeth* test requires the factfinder to speculate about hypothetical scenarios using inferences drawn from historical facts,

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[162] *See Wyeth*, 555 U.S. at 570-71 ("[T]hrough many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times."); 21 U.S.C. § 355(o)(4)(I) ("Rule of construction" clarifying that the 2007 FDCA amendments "shall not be construed to affect the responsibility of the responsible person . . . to maintain its label in accordance with existing requirements").

reasonable jurors could reach a broad range of conclusions when confronted with this record. To that inherent uncertainty we then add all the reasonable inferences that Rule 56 requires us to draw in Plaintiffs' favor: the FDA would have agreed that the evidence of an association was "reasonable" prior to 2010; the FDA rejected Merck's proposed warning because it was primarily concerned with the misleading references to stress fractures rather than the underlying science; the FDA refrained from counter-proposing an acceptable warning in 2009 because it considered it Merck's responsibility to submit a revised warning; the FDA affirmatively reached out to Merck in 2010 because it recognized that the science was now so strong that amending the label was a legal imperative, not because it was acknowledging a sufficient risk for the first time.

A reasonable juror reviewing the evidence in this case could find it less than highly probable that the FDA would not have approved a warning about the risk of atypical femur fractures that eliminated or revised references to "stress fractures." Accordingly, Merck is not entitled to summary judgment on its preemption defense to Plaintiffs' Warnings and Precautions claims.[163]

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[163] Our ruling today concerns only the correctness of the District Court's March 24, 2014 decision that Merck was entitled to summary judgment on its affirmative preemption defense. We express no view as to whether or how our ruling should be applied to any individual action in the MDL going forward.

One of the reasons Merck gave for treating *Wyeth* preemption as a pure question of law was that doing so would allegedly ensure

C. Merck is Not Entitled to Summary Judgment on Plaintiffs' Adverse Reactions Claims

Plaintiffs' failure-to-warn claims focus primarily on the assertion that Merck should have added a fractures warning to the Warnings and Precautions

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consistency of its application across the hundreds of claims in this MDL. We of course do not decide issues by considering how many lawsuits our ruling will extinguish or revive. At any rate, the suits in this MDL pose numerous binary jury questions that conceivably apply across the board. Fosamax either causes atypical femoral fractures or it does not; Merck either knew about the alleged risks of fracture or it did not; the risks of Fosamax either outweighed its benefits or they did not; the list goes on. Ontologically speaking, there is an "objective" right answer to each of these questions that does not vary from case to case. And treating each issue as one of pure law to be disposed at a swoop of the judge's pen would certainly speed matters along. But neither consideration is an adequate basis to shift the traditional line between judge and jury functions. Of course, if the manufacturer shows that there is no genuine dispute as to any material fact bearing on *Wyeth* preemption, then a judge can indeed decide as a matter of law that the defense is established. But that showing was not made here. The FDA either would have approved Plaintiffs' warning or they would not; we cannot say.

Treating preemption as a jury issue does not automatically condemn Merck to a thousand individual jury trials. The MDL parties could, for example, hold a bellwether trial on the preemption question, after which the prevailing party would be free to argue that the other side should be collaterally estopped from re-litigating preemption in individual cases. *See Markman*, 517 U.S. at 391 (recognizing that treating a question as a factual issue does not leave it "wide open in every new court" because "principles of issue preclusion would ordinarily foster uniformity"). Again, we express no view on the merits or likely outcomes of such an approach.

section of the Fosamax label prior to September 2010. But Plaintiffs also contend that their failure-to-warn claims encompass a related but distinct allegation that Merck should have added atypical fractures to the Adverse Reactions section prior to May 2009 (the date the FDA actually approved Merck's addition of atypical fractures to the Adverse Reactions section), and that Merck's failure to do so proximately caused their injuries.[164] The District Court ruled that this claim was insufficiently pled and not supported by the evidence, and entered summary judgment for Merck on the merits. This ruling was in error.

As an initial matter, the Adverse Reaction Claims are not preempted by *Wyeth*, and Merck does not argue otherwise. Merck requested that atypical fractures be added to the Adverse Reactions section in 2009, and the FDA approved the request. Merck has not shown by clear evidence that the FDA would have rejected such a warning had Merck proposed it earlier.

Turning to the merits, the District Court dismissed the Adverse Reactions claims on two grounds.[165] The

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[164] *See* A 1501.

[165] Although it does not appear to have been a basis for its decision, the District Court observed that a large number of Plaintiffs alleged injuries occurring after the FDA added the Adverse Reactions warning. According to the District Court, these Plaintiffs would only be able to assert a failure-to-warn claim based on the absence of a warning in the Warnings and Precautions section of the label. We disagree, as these Plaintiffs remain free to argue that their injuries were caused by their *use* of Fosamax prior to the addition of the Adverse Reactions warning.

first basis for the District Court's ruling was its conclusion that Plaintiffs did not specifically plead a failure-to-warn claim based on the Adverse Reactions label section in any of their complaints. Whether or not this is an accurate assessment—we do not have every MDL complaint before us to confirm, and there is no indication that the District Court reviewed each of the hundreds of complaints at issue either—we think it beside the point. Plaintiffs direct us to a number of complaints alleging generally that the Fosamax label did not adequately warn patients and doctors of the fracture risk, without specifying the particular warnings that should have been included or the particular failings of each label section.[166] The parties and the District Court all accept that these general allegations adequately pled the Warnings and Precautions theory discussed above. It is therefore difficult to understand why the District Court faulted the same complaints for failing to specify every section of the label that should have included a warning. At any rate, such specificity is not required by the Federal Rules of Civil Procedure.[167] Merck does not argue that the complaints failed to put it on notice of the Adverse Reactions claim, and that concession closes the door on any claim that the complaints themselves failed to adequately plead the Adverse Reactions theory.

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[166] *See* A 2245 ¶ 54, 2249 ¶ 76, 2190 ¶ 123, 2333 ¶ 57.

[167] *See Oneida Indian Nation v. Cty. of Oneida*, 617 F.3d 114, 132 (2d Cir. 2010) (complaint need not specify the legal theory underlying its claims so long as it contains sufficient facts to support liability); *Kirksey v. R.J. Reynolds Tobacco Co.*, 168 F.3d 1039, 1041 (7th Cir. 1999) (same).

The District Court also stated, without elaboration, that Plaintiffs had failed to "set forth evidence indicating that any doctor would not have prescribed Fosamax if the occurrence of low-energy femoral shaft fractures had been mentioned in the Adverse Reactions section prior to 2009."[168] Even if true, this does not justify summary judgment on the merits. The proper inquiry for summary judgment purposes is whether there was sufficient evidence to permit a reasonable juror to conclude that a doctor would not have prescribed Fosamax if fracture language had been added to the Adverse Reactions section prior to 2009. To this end, Plaintiffs submitted several declarations from their treating physicians declaring that if they had been informed that Fosamax posed a risk of femoral fractures, they likely would not have prescribed Fosamax or likely would have discontinued treatment.[169] These declarations do not specify which sections of the label should have contained such a warning. A reasonable juror could conclude that some of these physicians would not have prescribed Fosamax if atypical femur fractures had been listed in the Adverse Reactions section. Accordingly, the District Court should not have granted Merck summary judgment on the merits of Plaintiffs' Adverse Reactions failure-to-warn claims.

There is a deeper problem lurking in the District Court's decision to grant Merck a merits judgment in all of the MDL cases. A mass tort MDL is not a class action. It is a collection of separate lawsuits that are

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[168] Summary Judgment Order, 2014 WL 1266994, at *15.

[169] *See, e.g.*, A 792 ¶ 10, 794 ¶ 9, 796-97 ¶ 9, 798 ¶ 8.

coordinated for pretrial proceedings—and *only* pretrial proceedings—before being remanded to their respective transferor courts.[170] Some purely legal issues may apply in every case. But merits questions that are predicated on the existence or nonexistence of historical facts unique to each Plaintiff—*e.g.*, whether a particular Plaintiff's doctor would have read a warning in the Adverse Reactions section and ceased prescribing Fosamax as a result—generally are not amenable to across-the-board resolution. Each Plaintiff deserves the opportunity to develop those sort of facts separately, and the District Court's understandable desire to streamline proceedings cannot override the Plaintiffs' basic trial rights.[171] As a technical matter, Merck's *actual* burden at the summary judgment stage was to prove that there is no genuine dispute in *every single MDL case* that Plaintiffs' doctors would have continued to prescribe Fosamax even if the fracture warning had been added to the Adverse Reactions section before May 2009. It could not do so, and the District Court's grant of summary judgment on the merits was therefore erroneous.

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[170] 28 U.S.C. § 1407(a).

[171] The District Court and the parties could have, but did not, choose to have the Plaintiffs assemble a single "master complaint" that superseded the individual complaints. *See In re Refrigerant Compressors Antitrust Litig.*, 731 F.3d 586, 590-91 (6th Cir. 2013).

D. Merck is Not Entitled to Summary Judgment on Plaintiffs' Non-Warning Claims

The District Court held that Plaintiffs' Non-Warning Claims sounded in failure to warn and were therefore preempted to the same extent as the Warning and Precautions Claims. Accordingly, our decision vacating the District Court's preemption ruling as to the Warnings and Precautions Claims reinstates the Non-Warning Claims as well.[172] We pass no judgment on the merits of those claims or on whether they do in fact sound in failure to warn.

IV. CONCLUSION

For the foregoing reasons, we will vacate the District Court's grant of summary judgment to Merck and remand for further proceedings consistent with this opinion.

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[172] Merck argues that the non-warning claims are separately preempted by the Supreme Court's decision in *Mutual Pharmaceutical Co. v. Bartlett*, 133 S. Ct. 2466 (2013). Merck admits, however, that it did not raise this argument below—indeed, Merck appears to have explicitly disavowed the argument so it could characterize its defense as being based solely on *Wyeth*. Merck Br. 68; A 1727-28. "It is well established that arguments not raised before the District Court are waived on appeal." *DIRECTV Inc. v. Seijas*, 508 F.3d 123, 125 n.1 (3d Cir. 2007). We see no reason to deviate from that rule here.

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Cooper, Eva	14-2262	3-12-cv-00622
Delagarza, Margaret	14-2263	3-12-cv-00623

Shapiro, Ellen	14-2264	3-12-cv-00625
Frangos, Artemis	14-2265	3-12-cv-00626
Freelin, Stephanie	14-2266	3-12-cv-00627
Grassel, Sara	14-2267	3-12-cv-00628
Halpern, Beverly	14-2268	3-12-cv-00629
Harvey, Robert	14-2269	3-12-cv-00631
Jones, Renae	14-2270	3-12-cv-00640
Singh, Priscilla	14-2271	3-12-cv-00643
Worthington, Renee	14-2272	3-12-cv-00644
Palmer, Richard	14-2273	3-12-cv-00645
James, Claudia	14-2274	3-12-cv-00647
Kozloski, Margaret	14-2275	3-12-cv-00648
Matthews, Roxie Mo[gler]	14-2276	3-12-cv-00649
Newman, Lula	14-2277	3-12-cv-00650
Dirks, Susan	14-2278	3-12-cv-00651
Carpenter, Julia Ann	14-2279	3-12-cv-00654
Madary, Roberta	14-2280	3-12-cv-00655
Rimstidt, Nelda	14-2281	3-12-cv-00656
Taylor, Sherri	14-2282	3-12-cv-00657
Balsam, Barbara	14-2283	3-12-cv-00658
Mester, Dorothy	14-2284	3-12-cv-00659
Raven, Arleen	14-2285	3-12-cv-00660
Garrett, Barbara	14-2286	3-12-cv-00663
Dwyer, Marion	14-2287	3-12-cv-00664
Eck, Marlene	14-2288	3-12-cv-00665

Uselton, Lynnita	14-2289	3-12-cv-00666
Still, Nanette	14-2290	3-12-cv-00667
Wheeler, Jo	14-2291	3-12-cv-00688
Smith, Richard	14-2292	3-12-cv-00689
Bucher, Rose	14-2293	3-12-cv-00690
Giarratano, Ruth	14-2294	3-12-cv-00691
Goheen, Patty	14-2295	3-12-cv-00692
Powers, Peggy	14-2296	3-12-cv-00693
Muller, Eleanor	14-2297	3-12-cv-00694
Lemley, Sheila	14-2298	3-12-cv-00695
Curry, Nellie	14-2299	3-12-cv-00707
Thomas-Walsh, Ther[esa]	14-2300	3-12-cv-00714
Swanson, Nancy	14-2301	3-12-cv-00715
Erickson, Doris	14-2302	3-12-cv-00750
Pearson, Linda	14-2303	3-12-cv-00762
Underhill, Mary Lee	14-2304	3-12-cv-00789
Nord, Elayne Barbara	14-2305	3-12-cv-00790
Bryant, Jane	14-2306	3-12-cv-00791
Ciraolo, Joanna	14-2307	3-12-cv-00855
Savoy, Josephine	14-2308	3-12-cv-00928
Gentile, Emma	14-2309	3-12-cv-00936
Factor, Rosalyn Rena	14-2310	3-12-cv-00943
Walker, Sherry	14-2311	3-12-cv-00950
McCune, Bonnie	14-2312	3-12-cv-00974
Meldon, Virginia	14-2313	3-12-cv-01009

Greenberg, Carla	14-2314	3-12-cv-01013
Armstrong, Bobbie	14-2315	3-12-cv-01020
Garman, Rose Ann	14--2316	3-12-cv-01021
Goggin, Carol	14-2317	3-12-cv-01035
Goodman, Susan Jan[e]	14-2318	3-12-cv-01036
Drouet, Renee	14-2319	3-12-cv-01038
Stroh, Kerry	14-2320	3-12-cv-01065
Medina, Laarni	14-2321	3-12-cv-01075
Whitman, Ethel	14-2322	3-12-cv-01093
D'Angelo, Kimiko	14-2323	3-12-cv-01107
Hollander, Carol	14-2324	3-12-cv-01111
Harrow, Ronnie	14-2325	3-12-cv-01132
Hardy, Yvette	14-2326	3-12-cv-01133
Lynn, Vivian	14-2327	3-12-cv-01134
Hill, Laura Lee	14-2328	3-12-cv-01135
Gitter, Blossom	14-2329	3-12-cv-01177
Clow, Edna	14-2330	3-12-cv-01179
Hulik, Linda	14-2331	3-12-cv-01180
Lyons, Janet	14-2332	3-12-cv-01181
Fitzpatrick, Nora	14-2333	3-12-cv-01185
Suehiro, Tokia	14-2334	3-12-cv-01186
Brown, Linton	14-2335	3-12-cv-01187
Seims, Marcie	14-2336	3-12-cv-01200
Andrejasich, Anne	14-2337	3-12-cv-01203
Edwards, Sally	14-2338	3-12-cv-01204

Kakareka. Edith	14-2339	3-12-cv-01205
Jones, Denman	14-2340	3-12-cv-01220
Morris. Joyce	14-2341	3-12-cv-01221
Murphy, Cheryl	14-2342	3-12-cv-01222
Spires, Evelyn	14-2343	3-12-cv-01277
Davis, Anna M.	14-2345	3-12-cv-01322
Jefferies, Gail	14-2346	3-12-cv-01325
Ross, Betty Jo	14-2347	3-12-cv-01326
Jepson, Norma	14-2348	3-12-cv-01327
Fifer, Ladonna	14-2349	3-12-cv-01328
Moore, Marlene	14-2350	3-12-cv-01329
Bryant, Sharon	14-2351	3-12-cv-01344
Bishop, Rosemary	14-2352	3-12-cv-01356
Burleson, Jacqueline	14-2354	3-12-cv-01373
Fenton, Carole	14-2355	3-12-cv-01387
Yost, Marilyn	14-2356	3-12-cv-01395
Richard-Amato, Patri[cia]	14-2357	3-12-cv-01397
Wang, Su-Mei	14-2358	3-12-cv-01398
Zimmerman, Martha [Farr]	14-2359	3-12-cv-01399
Flower, Gail	14-2360	3-12-cv-01410
Cross, Katherine	14-2361	3-12-cv-01449
Mejia, Teresita	14-2362	3-12-cv-01450
Agrow, Rosalie	14-2363	3-12-cv-01468
Crook, Patricia	14-2364	3-12-cv-01476
Courville, Paula	14-2365	3-12-cv-01484

Bielecky, Margaret	14-2366	3-12-cv-01487
Wright, Judith	14-2367	3-12-cv-01549
Hayes, Mavis	14-2368	3-12-cv-01552
Hanson, Nelda	14-2369	3-12-cv-01566
Stencler, Roxanna	14-2370	3-12-cv-01567
Lowell, Sarah	14-2371	3-12-cv-01568
Collier, Marion	14-2372	3-12-cv-01569
Waldrup, Roberta	14-2373	3-12-cv-01715
Bohn, Edward []	14-2375	3-12-cv-01754
Freay, Onnolee	14-2376	3-12-cv-01817
Sheehan, Yvonne T[.]	14-2377	3-12-cv-01845
Merrell, Preston	14-2378	3-12-cv-01846
Jones, Alice	14-2379	3-12-cv-01847
Fracaro, Fern Lee	14-2380	3-12-cv-01849
McKelvey, Elizabeth	14-2381	3-12-cv-01850
Keaser, Barbara	14-2382	3-12-cv-01875
Brenner, Lois	14-2383	3-12-cv-01876
Azar, Bernice	14-2384	3-12-cv-01967
Hubbard, Linda	14-2385	3-12-cv-01975
Arnold, Doris	14-2386	3-12-cv-01996
Halligan, Carla	14-2387	3-12-cv-01997
Frei, Miryam	14-2388	3-12-cv-01998
Besser, Deborah []	14-2389	3-12-cv-01999
Dandridge, Earlene	14-2390	3-12-cv-02000
Weissberger, Kathryn	14-2391	3-12-cv-02002
Stone, Harriet	14-2392	3-12-cv-02048

Pustilnik, Jean	14-2393	3-12-cv-02121
Pickett, Theodore	14-2394	3-12-cv-02127
Bowden, Gregory	14-2395	3-12-cv-02150
Kniffen. Donna	14-2396	3-12-cv-02159
Mayer, Christine	14-2397	3-12-cv-02210
Lynch, Kiersten	14-2398	3-12-cv-02211
Dunn, Lucille	14-2399	3-12-cv-02258
Nelson, Susan	14-2400	3-12-cv-02265
Lindenmeier, Janet	14-2401	3-12-cv-02302
Frye, Barbara	14-2402	3-12-cv-02371
Sandfort, Irma	14-2403	3-12-cv-02451
Odum, Connie	14-2404	3-12-cv-05581
Latta, Theresa	14-2405	3-12-cv-02559
Kirkpatrick, Judy	14-2406	3-12-cv-02560
Canaday, Connie	14-2407	3-12-cv-02561
Edwards, Donna	14-2408	3-12-cv-02594
Lackey, Karen	14-2409	3-12-cv-02596
Evans, Dorothy	14-2410	3-12-cv-02598
Brown, Towanda	14-2411	3-12-cv-02600
Tressler, Vera	14-2412	3-12-cv-02647
Heldberg, Judith	14-2413	3-12-cv-02771
Hen, Azucena	14-2414	3-12-cv-02833
Sias, Diana Van Pelt	14-2415	3-12-cv-02837
Otto, Harriet	14-2416	3-12-cv-02838
Best, Bettie	14-2417	3-12-cv-03017
Davis, Betty Saki	14-2418	3-12-cv-03021

Roberts, Margaret	14-2419	3-12-cv-03022
Goias, Geraldine	14-2420	3-12-cv-03023
Lona, Lucille	14-2421	3-12-cv-03025
McMurray, Deborah	14-2422	3-12-cv-03026
Doriott, Angelita	14-2423	3-12-cv-03027
Thieman, Donna	14-2424	3-12-cv-03259
White, Claudia	14-2425	3-12-cv-03260
Eshelman, Stephanie	14-2426	3-12-cv-03261
Grillo, Maria	14-2427	3-12-cv-03286
Stefanowski, Lucy	14-2428	3-13-cv-07894
Burghardt, Pamela	14-2429	3-12-cv-03326
Gerber, Marilyn	14-2430	3-12-cv-03328
Tong, Lucy	14-2431	3-12-cv-03329
Venner, Vida	14-2432	3-12-cv-03330
Uslan, Sharon	14-2433	3-12-cv-03331
Goldberg, Ethel	14-2434	3-12-cv-03335
Hudson, Laraine	14-2435	3-12-cv-03345
Rittenhouse, Carolyn	14-2436	3-12-cv-03346
Budd, Randal	14-2437	3-12-cv-03347
Myers, Eva	14-2438	3-12-cv-03348
Dykes, Marsha	14-2439	3-12-cv-03358
Foree, Edith	14-2440	3-12-cv-3366
Indich, Terry	14-2441	3-12-cv-03399
Travor, Lois Annette	14-2442	3-12-cv-03429
Steen, Barbara	14-2443	3-12-cv-03511
Charms, Shirley	14-2444	3-12-cv-03696

Denham, Janice	14-2445	3-12-cv-03705
Tanglao, Lourdes	14-2446	3-12-cv-03730
Disosway, Linda	14-2447	3-12-cv-03769
Lare, Sandra	14-2448	3-12-cv-03770
Nealen, Arlene	14-2449	3-12-cv-03789
DerHarootunian, Car[olyn]	14-2450	3-12-cv-03795
Yacoub, Caroline	14-2452	3-12-cv-03878
Baker, Alma	14-2453	3-12-cv-03879
Palma, Lucita	14-2454	3-12-cv-03904
Mateo, Yoshie	14-2455	3-12-cv-03939
Terranova. Patricia	14-2456	2-12-cv-03959
Hill, Mary	14-2457	3-12-cv-04014
Wilson, Selma	14-2458	3-12-cv-04190
Toland Kathleen	14-2459	3-12-cv-04423
Fillippello, Margaret	14-2460	3-12-cv-04424
Harris, Ramona	14-2461	3-12-cv-04426
Lane, Sharon	14-2462	3-12-cv-04440
Whisenant, Louise	14-2463	3-12-cv-04453
Carter, Joan	14-2464	3-12-cv-04454
Glenn, Sue	14-2465	3-12-cv-04566
Sweet, Karen	14-2466	3-12-cv-04599
Hutton, Nancy	14-2467	3-12-cv-04601
Hernandez, Antonia	14-2468	3-12-cv-04604
Favor, Judith	14-2469	3-12-cv-04611
Parker, Esther	14-2471	3-12-cv-04638

Mitchell, Cheryl	14-2472	3-12-cv-04656
Paralikis, Pamela	14-2473	3-12-cv-04663
Bottari, Donna	14-2474	3-12-cv-04664
Hedgepeth, Betty	14-2475	3-12-cv-04721
Sperber, Bernice	14-2476	3-12-cv-04760
Currie, Marlene	14-2477	3-12-cv-04762
Worthington, Jerrene	14-2478	3-12-cv-04773
Patrina, Chester []	14-2479	3-12-cv-04802
Falcone, Patricia	14-2480	3-12-cv-04806
Anselmo, Victoria	14-2481	3-12-cv-04836
Patterson, Ethel	14-2482	3-12-cv-05018
Haslam, Martha	14-2483	3-12-cv-05019
Julius, Diana	14-2484	3-12-cv-05020
Mott, Leann	14-2485	3-12-cv-05060
Theberge, Jeanne	14-2486	3-12-cv-05085
Walker, Shirley	14-2487	3-12-cv-05094
Bedsworth, Alan []	14-2488	3-12-cv-05108
Crew, Nellie	14-2489	3-12-cv-05205
Astrug, Debra	14-2490	3-12-cv-05269
Dixon, Carolyn	14-2491	3-12-cv-05271
Edgil-Rogers, Judee	14-2492	3-12-cv-05297
Gilmer, Marjorie	14-2493	3-12-cv-05364
Kovalick, Carole	14-2494	3-12-cv-05383
Knutson, Josephine	14-2495	3-12-cv-05384
Smith, Regina	14-2496	3-12-cv-05385

Hamilton-Gamman, S[andra]	14-2497	3-12-cv-05389
Needles, Josephine	14-2498	3-12-cv-05391
Kendrick. Billie	14-2499	3-12-cv-05392
Paxton, Mary	14-2500	3-12-cv-05393
Stanwood, Peggy	14-2501	3-12-cv-05485
Knopick, Carol	14-2502	3-12-cv-05557
Osburn, Gaile	14-2503	3-12-cv-05560
Miller, Dolores	14-2504	3-12-cv-02549
Heckard, Shirley	14-2505	3-12-cv-05681
Cline, Diane	14-2506	3-12-cv-05776
Cummings, Sarah	14-2507	3-12-cv-05975
Jodszuweit, Armida	14-2508	3-12-cv-05978
Collier, Nancy	14-2509	3-12-cv-05993
Sayers, Sheila	14-2510	3-12-cv-06028
Cook. Shirley	14-2511	3-12-cv-06029
Wiegand, Mary	14-2512	3-12-cv-06155
Roland, Annie	14-2513	3-12-cv-06182
Bridgeman, Max	14-2514	3-12-cv-06187
Wong, Anita	14-2515	3-12-cv-06191
Hayden, Jane	14-2516	3-12-cv-06192
McGrath, Sheila	14-2517	3-12-cv-06216
Van Blaricom, Betty	14-2518	3-12-cv-06237
Thomas, Eugune Mid[dleton]	14-2519	3-12-cv-06264
Fuerstnau, Barbara	14-2520	3-12-cv-06266
Halfmann, Mary	14-2521	3-12-cv-06267

Kimizuka, Yoshie	14-2522	3-12-cv-06269
Hofmann, Kathleen	14-2523	3-12-cv-06275
Duggan, Doris	14-2524	3-12-cv-06289
Andorka-Aceves, Deb[orah]	14-2525	3-12-cv-06301
Herndon, Lucy Mae	14-2526	3-12-cv-06351
Delikat. Ellen	14-2527	3-12-cv-06365
Mouser, Donna	14-2528	3-12-cv-06366
Hulsman, Elaine	14-2529	3-12-cv-06376
Kempfer, Faye	14-2530	3-12-cv-06377
Lotter, Dolores	14-2531	3-12-cv-06378
Cummings, Irene Lilli[an]	14-2532	3-12-cv-06397
Irving, Zepher	14-2533	3-12-cv-06430
Marcus, Rita	14-2534	3-12-cv-06432
Halpern, Marion	14-2535	3-12-cv-06433
Ogle, Ann	14-2536	3-12-cv-06434
Bittner, Marcella	14-2537	3-12-cv-06437
Wade, Kay	14-2538	3-12-cv-06439
Ahern, Frances	14-2539	3-12-cv-06443
Boshell, Marsha	14-2540	3-12-cv-06444
Sandt, Faye	14-2541	3-12-cv-06445
Holmes, Leanne	14-2542	3-12-cv-06446
Napoli, Anna	14-2543	3-12-cv-06450
Vaughn, Patricia	14-2544	3-12-cv-06451
Irizarry, Sheila	14-2545	3-12-cv-06453
Kort, Barbara	14-2546	3-12-cv-06454

Kosvick. Melinda	14-2547	3-12-cv-06455
Homa. Barbara	14-2548	3-12-cv-06456
Stepanski, Mary Jo	14-2549	3-12-cv-06457
Lare, Barbara	14-2550	3-12-cv-06458
Nguyen, Susan	14-2551	3-12-cv-06459
Jeet, Lalita	14-2552	3-12-cv-06460
Naik, Khadijah	14-2553	3-12-cv-06461
Bartlett, Ann	14-2554	3-12-cv-06462
Aydin. Jean	14-2555	3-12-cv-06463
Dowd, Jeanette	14-2556	3-12-cv-06464
Van Gosen, Helen	14-2557	3-12-cv-06465
Huddleston, Shirley	14-2558	3-12-cv-06466
Griffin. Jennifer	14-2559	3-12-cv-06469
Crisci, Stephen N. []	14-2560	3-12-cv-06550
Jones, Geraldine	14-2561	3-12-cv-06711
McKinney, Carlene	14-2562	3-12-cv-06719
Karantza, John	14-2563	3-12-cv-06770
Bozue, Dorothy	14-2564	3-12-cv-06840
Cline, Beatrice	14-2565	3-12-cv-06841
Broadstone, Judith	14-2566	3-12-cv-06845
Schmitt, Luise Gerlin[de]	14-2567	3-12-cv-06846
Cherco. Patricia	14-2568	3-12-cv-06850
Neuman, Janet	14-2569	3-12-cv-06859
Isom, Leann	14-2570	3-12-cv-06860
Heiny, Joyce	14-2571	3-12-cv-06863

Vertuccio, Lana	14-2572	3-12-cv-06877
Williams, Susanne	14-2573	3-12-cv-06899
Stevenson, Nada	14-2574	3-12-cv-06900
Elison, Linda	14-2575	3-12-cv-06901
Lingo, Melba	14-2576	3-12-cv-06903
Baylor, Richard	14-2577	3-12-cv-06905
Thompson, Loralee	14-2578	3-12-cv-06907
Miller, Esther	14-2579	3-12-cv-06952
Orr, June	14-2580	3-12-cv-06954
Maki, Gale	14-2581	3-12-cv-06955
Collins, John	14-2582	3-12-cv-06956
McAnulty, Joan	14-2583	3-12-cv-06957
Abney, Virginia	14-2584	3-12-cv-07023
Altson, Amy	14-2585	3-12-cv-07048
Harris, Hope []	14-2586	3-12-cv-07443
Jaeger, Bernadette	14-2587	3-12-cv-07819
Couture, Diane	14-2588	3-13-cv-00001
VanDyke, Patricia	14-2589	3-13-cv-00137
Antoff, Christine	14-2590	3-13-cv-00171
Wyly, Lois Ann	14-2592	3-13-cv-00442
Conner, Cheryl	14-2593	3-13-cv-00718
Kardon, Koula	14-2594	3-13-cv-00720
Bialkowski, Mary	14-2595	3-13-cv-00816
Affronti, Joanne	14-2599	3-13-cv-00818
Bannon, Gladys	14-2600	3-13-cv-00894
Golden, Jane	14-2601	3-13-cv-00926

Pitts, Shirley Ann	14-2602	3-13-cv-00928
Slinkman, William Ric[hard]	14-2603	3-13-cv-01062
Albert, Elizabeth	14-2604	3-13-cv-01063
Hawk, Joycelyn	14-2605	3-13-cv-01071
Pritchard, Helen	14-2606	3-13-cv-01215
Myers, Susan	14-2607	3-13-cv-01314
Brooks, Betty	14-2608	3-13-cv-01337
Hawkins, Amy	14-2609	3-13-cv-01340
Edmondson, Maxine	14-2610	3-13-cv-01352
Kamienski, Mary	14-2611	3-13-cv-01369
Neuman, Delores	14-2612	3-13-cv-01370
Peters, Alohoa	14-2613	3-13-cv-01371
Routhieaux, Marguer[itte]	14-2614	3-13-cv-01378
Alberg, Evelyn	14-2615	3-13-cv-01415
Goodman, Carol Ann	14-2616	3-13-cv-01476
Samuelson, Johann	14-2618	3-13-cv-01884
Rudolph, Joyce	14-2619	3-13-cv-02616
Romeo, Alice	14-2620	3-13-cv-02617
Grems, Mary	14-2621	3-13-cv-2649
McKeon-Cincotta, Le[na]	14-2622	3-13-cv-02735
Jernigan, Mary Lou	14-2623	3-13-cv-02827
Wicker, Marie	14-2624	3-13-cv-02836
Stampliakis, Helen	14-2625	3-13-cv-02958
Crook, Judith	14-2626	3-13-cv-03211

London, Phyllis	14-2627	3-13-cv-03342
Connor, Ruth	14-2628	3-13-cv-03353
Mulqueen, Mary	14-2629	3-13-cv-03474
Bergmann, Ruth	14-2630	3-13-cv-03741
Spallone, Josephine	14-2631	3-13-cv-03929
Maddern, Karen	14-2632	3-13-cv-04075
Marcelles, Sara	14-2634	3-13-cv-05984
Tolston, Betty	14-2635	3-13-cv-06090
Oakes, Miriam	14-2636	3-11-cv-05082
Murphy, Nancy	14-2813	3-12-cv-06282
Gaynor, Barbara	14-3267	3-12-cv-01492

APPENDIX B

UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

No. 14-1900 et al

In re: Fosamax (Alendronate Sodium) Product Liability Litigation

ORDER AMENDING APPENDIX A TO OPINION

Due to inadvertent clerical errors, Appendix A to the opinion was missing one appeal number (14-3220) and a lower court number (08-cv-00008). The Appendix has been revised and the corrected version will be filed as an attachment to this order.

For the Court,

s/ Marcia M. Waldron
Clerk

Dated: April 11, 2017
PDB/cc: All Counsel of Record

Appendix A

Case Name	Appeal No.	DNJ No.
Albrecht, Doris	14-1900	3-12-cv-03287
Molnar, Phyllis	14-2109	3-08-cv-00008
Gozdziak, Margaret	14-2110	3-09-cv-05630
Duke, Dolores	14-2111	3-09-cv-05693
Schultz, Susan	14-2112	3-08-cv-03545
Hines, Cynthia	14-2113	3-10-cv-04839
Goodwin, Joan	14-2114	3-10-cv-05461
Moline, Barbara	14-2115	3-10-cv-05462
Wheeler, Kathryn	14-2117	3-10-cv-06282
Denker, Elayne	14-2118	3-11-cv-00033
Heaton, Nancy	14-2119	3-11-cv-00570
Bonne, Virginia	14-2120	3-11-cv-00571
Lefebvre, Alice	14-2121	3-11-cv-00586
Hogan, Marie	14-2122	3-11-cv-00587
Karch, Lillie	14-2123	3-11-cv-00589
Walraed, Susan	14-2124	3-11-cv-00869
Kolb, Lauren	14-2126	3-11-cv-01498
Dematto, Mary	14-2127	3-11-cv-01886
Germino, Virginia Lee	14-2128	3-11-cv-03165
Chaires, Jeanette	14-2129	3-11-cv-03168
Salvatore, Sheila	14-2130	3-11-cv-03169
Collins, Lucille	14-2131	3-11-cv-03170
Miller, Betty	14-2132	3-11-cv-03174
Young, Marilyn	14-2133	3-11-cv-03225
Sunshine, Beverly	14-2134	3-11-cv-03309
Sutton, Barbara	14-2135	3-11-cv-03310
Granato, Irene	14-2136	3-11-cv-03369
Graves, Barbara	14-2137	3-11-cv-03645
Brown, Elizabeth	14-2138	3-11-cv-03867
Van, Mary Evelyn	14-2139	3-11-cv-03911

Zessin, Deloris	14-2140	3-11-cv-03919
Wirth, Carol	14-2141	3-11-cv-03930
Lyman, Patricia	14-2142	3-11-cv-04160
Foley, Peggy	14-2143	3-11-cv-04171
O'Brien, Molly	14-2144	3-11-cv-04242
O'Brien, Molly	14-2145	3-11-cv-04242
Evans, Laura	14-2146	3-11-cv-04277
Krieg, Julia	14-2147	3-11-cv-04956
Cortez, Lorice	14-2148	3-11-cv-05025
Hardy, Shirley	14-2149	3-11-cv-05077
Marks, Martha	14-2150	3-11-cv-05079
Grassucci, Shirley	14-2151	3-11-cv-05083
Clougherty, Mary Pat[ricia]	14-2153	3-11-cv-05295
Edwards, Sybil	14-2154	3-11-cv-05300
Johnson, Susan	14-2155	3-11-cv-05301
Onaka, Eleanor	14-2156	3-11-cv-05302
Scott, Sylvia	14-2157	3-11-cv-05303
Whitt, Betty Jean	14-2158	3-11-cv-05335
Penigian, Jean	14-2159	3-11-cv-05703
Berlin, Ruth	14-2160	3-11-cv-05720
Collins, Joann	14-2161	3-11-cv-05826
Brogna, Loretta	14-2162	3-11-cv-05912
Hodge, Helen	14-2163	3-11-cv-06162
Stark, Vivian	14-2164	3-11-cv-06164
Voss, Betty	14-2165	3-11-cv-06347
Schornick, Lori []	14-2166	3-11-cv-06387
Panouis, Androniki	14-2167	3-11-cv-06411
Blackford, June	14-2168	3-11-cv-06415
Krakovitz, Pearl	14-2169	3-11-cv-06417
Pisarz, Josephine	14-2170	3-11-cv-06419
Strominger, Betty	14-2171	3-11-cv-06420
Schick, Joan	14-2172	3-11-cv-06421
Chee, Paula	14-2173	3-11-cv-06451

Gribben, Angela	14-2174	3-11-cv-06452
Ourecky, Roberta	14-2175	3-11-cv-06468
Price, Carolyn	14-2176	3-11-cv-06469
Howe, Elaine	14-2177	3-11-cv-06657
Care, Margaret	14-2178	3-11-cv-06694
Hanel, Kannika	14-2179	3-11-cv-06817
Standish, Debbie	14-2180	3-11-cv-06912
Wilkins, Edith	14-2181	3-11-cv-06945
Covey, Janet	14-2182	3-11-cv-06946
Radford, Shirley	14-2183	3-11-cv-06947
Poynor, Sherry	14-2184	3-11-cv-06948
Johnson, Janet	14-2185	3-11-cv-06959
Sontag, Marian	14-2186	3-11-cv-06983
Nelson, Edward	14-2187	3-11-cv-07020
Haviland, Barbara	14-2188	3-11-cv-07104
Matney, Rosemary	14-2189	3-11-cv-07145
McGill, Barbara	14-2190	3-11-cv-07185
Schwalbe, Linda	14-2191	3-11-cv-07208
Nation, Karleen	14-2192	3-11-cv-07345
Misner, Anita	14-2193	3-11-cv-07401
Burke, Louise	14-2194	3-11-cv-07429
Carter-Morcomb, Pat[ty]	14-2195	3-11-cv-07432
Messerli, Donna	14-2196	3-11-cv-07491
McKee, Eleanor	14-2197	3-11-cv-07493
Mayes, Claudice	14-2198	3-11-cv-07516
Joyce, Michael	14-2199	3-11-cv-07517
Hensley, Mary	14-2200	3-11-cv-07518
Degen, Patricia	14-2201	3-11-cv-07519
Mahan, Caroline	14-2202	3-11-cv-07520
Mistretta, Wilma	14-2203	3-11-cv-07521
Sorrentino, Theresa	14-2204	3-11-cv-07522
Tucker, Assunta	14-2205	3-11-cv-07523
Green, Mariella	14-2206	3-11-cv-07524

Greenway, Ann	14-2207	3-11-cv-07525
Ivey, Jane	14-2208	3-11-cv-07557
Driver, Virginia	14-2209	3-11-cv-07558
Juth, Joann	14-2210	3-11-cv-07613
Buitron, Catherine	14-2211	3-11-cv-007614
Wallis, Russell	14-2212	3-11-cv-07619
Carter, Ann	14-2213	3-12-cv-00012
Murphy, Betty	14-2214	3-12-cv-00014
Sutton, Catrinia []	14-2215	3-12-cv-00015
Duffy, Joan	14-2216	3-12-cv-00016
Pinkney, Lani	14-2217	3-12-cv-00017
Nagy, Norma	14-2218	3-12-cv-00018
Richardson, Lee	14-2219	3-12-cv-00019
Skinner, Leone	14-2220	3-12-cv-00021
Steinert, Julie	14-2221	3-12-cv-00022
Lopes, Mary	14-2222	3-12-cv-00023
Shepherd, Madge	14-2223	3-12-cv-00082
Pappas, Diane []	14-2224	3-12-cv-00168
Anderson, Barbara []	14-2225	3-12-cv-00227
Nesbitt, Craig	14-2226	3-12-cv-00268
Coventry, Melinda	14-2227	3-12-cv-00269
Adams, Brenda	14-2228	3-12-cv-00270
Yancu, Milly	14-2229	3-12-cv-00271
Franklin, Suzane	14-2230	3-12-cv-00272
Davis, Patricia	14-2231	3-12-cv-00273
Foland, Bobbie []	14-2232	3-12-cv-00278
Gerardo, Claudia	14-2233	3-12-cv-00310
Mueller, Eileen	14-2234	3-12-cv-00312
Held, Mary	14-2235	3-12-cv-00360
Weiss, Linda	14-2236	3-12-cv-00374
Hunt, Betty Burch	14-2237	3-12-cv-00375
Eisen, Ella	14-2239	3-12-cv-00391
Rangel, Elvia	14-2240	3-12-cv-00392

Thomasson, Patsy M[ay]	14-2241	3-12-cv-00403
Schendle, Carolyn	14-2242	3-12-cv-00404
Hogan, Charlotte	14-2243	3-12-cv-00464
Baldridge, Wilemina	14-2244	3-12-cv-00503
McCabe, Doreen	14-2245	3-12-cv-00504
McCabe, Judith	14-2246	3-12-cv-00508
Huenefeld, Catherine	14-2247	3-12-cv-00564
Gregori, Carolyn	14-2248	3-12-cv-00566
Heinonen, Marie	14-2249	3-12-cv-00567
Rath, Carolyn	14-2250	3-12-cv-00568
Rousey, Shirlie	14-2251	3-12-cv-00569
Simpson, Esther	14-2252	3-12-cv-00570
Wilson, Sharon	14-2253	3-12-cv-00571
Stotts, Wilma	14-2254	3-12-cv-00572
Everly, Myrna	14-2255	3-12-cv-00588
Kraynick, Judith	14-2256	3-12-cv-00589
Begany, Helen	14-2257	3-12-cv-00590
Finn, Barbara	14-2258	3-12-cv-00591
Scott, Lois	14-2259	3-12-cv-00592
Migatulski, Mary	14-2260	3-12-cv-000593
Reitz, Alice	14-2261	3-12-cv-00594
Cooper, Eva	14-2262	3-12-cv-00595
Delagarza, Margaret	14-2263	3-12-cv-00622
Shapiro, Ellen	14-2264	3-12-cv-00623
Frangos, Artemis	14-2265	3-12-cv-00625
Freelin, Stephanie	14-2266	3-12-cv-00626
Grassel, Sara	14-2267	3-12-cv-00627
Halpern, Beverly	14-2268	3-12-cv-00628
Harvey, Robert	14-2269	3-12-cv-00629
Jones, Renae	14-2270	3-12-cv-00631
Singh, Priscilla	14-2271	3-12-cv-00640
Worthington, Renee	14-2272	3-12-cv-00643
Palmer, Richard	14-2273	3-12-cv-00644

James, Claudia	14-2274	3-12-cv-00645
Kozloski, Margaret	14-2275	3-12-cv-00647
Matthews, Roxie Mo[gler]	14-2276	3-12-cv-00648
Newman, Lula	14-2277	3-12-cv-00649
Dirks, Susan	14-2278	3-12-cv-00650
Carpenter, Julia Ann	14-2279	3-12-cv-00651
Madary, Roberta	14-2280	3-12-cv-00654
Rimstidt, Nelda	14-2281	3-12-cv-00655
Taylor, Sherri	14-2282	3-12-cv-00656
Balsam, Barbara	14-2283	3-12-cv-00657
Mester, Dorothy	14-2284	3-12-cv-00658
Raven, Arleen	14-2285	3-12-cv-00659
Garrett, Barbara	14-2286	3-12-cv-00660
Dwyer, Marion	14-2287	3-12-cv-00663
Eck, Marlene	14-2288	3-12-cv-00664
Uselton, Lynnita	14-2289	3-12-cv-00665
Still, Nanette	14-2290	3-12-cv-00666
Wheeler, Jo	14-2291	3-12-cv-00667
Smith, Richard	14-2292	3-12-cv-00688
Bucher, Rose	14-2293	3-12-cv-00689
Giarratano, Ruth	14-2294	3-12-cv-00690
Goheen, Patty	14-2295	3-12-cv-00691
Powers, Peggy	14-2296	3-12-cv-00692
Muller, Eleanor	14-2297	3-12-cv-00693
Lemley, Sheila	14-2298	3-12-cv-00694
Curry, Nellie	14-2299	3-12-cv-00695
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Swanson, Nancy	14-2301	3-12-cv-00714
Erickson, Doris	14-2302	3-12-cv-00715
Pearson, Linda	14-2303	3-12-cv-00750
Underhill, Mary Lee	14-2304	3-12-cv-00762
Nord, Elayne Barbara	14-2305	3-12-cv-00789

Bryant, Jane	14-2306	3-12-cv-00790
Ciraolo, Joanna	14-2307	3-12-cv-00791
Savoy, Josephine	14-2308	3-12-cv-00855
Gentile, Emma	14-2309	3-12-cv-00928
Factor, Rosalyn Rena	14-2310	3-12-cv-00936
Walker, Sherry	14-2311	3-12-cv-00943
McCune, Bonnie	14-2312	3-12-cv-00950
Meldon, Virginia	14-2313	3-12-cv-00974
Greenberg, Carla	14-2314	3-12-cv-01009
Armstrong, Bobbie	14-2315	3-12-cv-01013
Garman, Rose Ann	14--2316	3-12-cv-01020
Goggin, Carol	14-2317	3-12-cv-01021
Goodman, Susan Jan[e]	14-2318	3-12-cv-01035
Drouet, Renee	14-2319	3-12-cv-01036
Stroh, Kerry	14-2320	3-12-cv-01038
Medina, Laarni	14-2321	3-12-cv-01065
Whitman, Ethel	14-2322	3-12-cv-01075
D'Angelo, Kimiko	14-2323	3-12-cv-01093
Hollander, Carol	14-2324	3-12-cv-01107
Harrow, Ronnie	14-2325	3-12-cv-01111
Hardy, Yvette	14-2326	3-12-cv-01132
Lynn, Vivian	14-2327	3-12-cv-01133
Hill, Laura Lee	14-2328	3-12-cv-01134
Gitter, Blossom	14-2329	3-12-cv-01135
Clow, Edna	14-2330	3-12-cv-01177
Hulik, Linda	14-2331	3-12-cv-01179
Lyons, Janet	14-2332	3-12-cv-01180
Fitzpatrick, Nora	14-2333	3-12-cv-01181
Suehiro, Tokia	14-2334	3-12-cv-01185
Brown, Linton	14-2335	3-12-cv-01186
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Andrejasich, Anne	14-2337	3-12-cv-01200
Edwards, Sally	14-2338	3-12-cv-01203

Kakareka, Edith	14-2339	3-12-cv-01204
Jones, Denman	14-2340	3-12-cv-01205
Morris, Joyce	14-2341	3-12-cv-01220
Murphy, Cheryl	14-2342	3-12-cv-01221
Spires, Evelyn	14-2343	3-12-cv-01222
Davis, Anna M.	14-2345	3-12-cv-01277
Jefferies, Gail	14-2346	3-12-cv-01322
Ross, Betty Jo	14-2347	3-12-cv-01325
Jepson, Norma	14-2348	3-12-cv-01326
Fifer, Ladonna	14-2349	3-12-cv-01327
Moore, Marlene	14-2350	3-12-cv-01328
Bryant, Sharon	14-2351	3-12-cv-01329
Bishop, Rosemary	14-2352	3-12-cv-01344
Burleson, Jacqueline	14-2354	3-12-cv-01356
Fenton, Carole	14-2355	3-12-cv-01373
Yost, Marilyn	14-2356	3-12-cv-01387
Richard-Amato, Patri[cia]	14-2357	3-12-cv-01395
Wang, Su-Mei	14-2358	3-12-cv-01397
Zimmerman, Martha [Farr]	14-2359	3-12-cv-01398
Flower, Gail	14-2360	3-12-cv-01399
Cross, Katherine	14-2361	3-12-cv-01410
Mejia, Teresita	14-2362	3-12-cv-01449
Agrow, Rosalie	14-2363	3-12-cv-01450
Crook, Patricia	14-2364	3-12-cv-01468
Courville, Paula	14-2365	3-12-cv-01476
Bielecky, Margaret	14-2366	3-12-cv-01484
Wright, Judith	14-2367	3-12-cv-01487
Hayes, Mavis	14-2368	3-12-cv-01549
Hanson, Nelda	14-2369	3-12-cv-01552
Stencler, Roxanna	14-2370	3-12-cv-01566
Lowell, Sarah	14-2371	3-12-cv-01567
Collier, Marion	14-2372	3-12-cv-01568

Waldrup, Roberta	14-2373	3-12-cv-01569
Bohn, Edward []	14-2375	3-12-cv-01715
Freay, Onnolee	14-2376	3-12-cv-01754
Sheehan, Yvonne T[.]	14-2377	3-12-cv-01817
Merrell, Preston	14-2378	3-12-cv-01845
Jones, Alice	14-2379	3-12-cv-01846
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McKelvey, Elizabeth	14-2381	3-12-cv-01849
Keaser, Barbara	14-2382	3-12-cv-01850
Brenner, Lois	14-2383	3-12-cv-01875
Azar, Bernice	14-2384	3-12-cv-01876
Hubbard, Linda	14-2385	3-12-cv-01967
Arnold, Doris	14-2386	3-12-cv-01975
Halligan, Carla	14-2387	3-12-cv-01996
Frei, Miryam	14-2388	3-12-cv-01997
Besser, Deborah []	14-2389	3-12-cv-01998
Dandridge, Earlene	14-2390	3-12-cv-01999
Weissberger, Kathryn	14-2391	3-12-cv-02000
Stone, Harriet	14-2392	3-12-cv-02002
Pustilnik, Jean	14-2393	3-12-cv-02048
Pickett, Theodore	14-2394	3-12-cv-02121
Bowden, Gregory	14-2395	3-12-cv-02127
Kniffen, Donna	14-2396	3-12-cv-02150
Mayer, Christine	14-2397	3-12-cv-02159
Lynch, Kiersten	14-2398	3-12-cv-02210
Dunn, Lucille	14-2399	3-12-cv-02211
Nelson, Susan	14-2400	3-12-cv-02258
Lindenmeier, Janet	14-2401	3-12-cv-02265
Frye, Barbara	14-2402	3-12-cv-02302
Sandfort, Irma	14-2403	3-12-cv-02371
Odum, Connie	14-2404	3-12-cv-02451
Latta, Theresa	14-2405	3-12-cv-05581
Kirkpatrick, Judy	14-2406	3-12-cv-02559
Canaday, Connie	14-2407	3-12-cv-02560

Edwards, Donna	14-2408	3-12-cv-02561
Lackey, Karen	14-2409	3-12-cv-02594
Evans, Dorothy	14-2410	3-12-cv-02596
Brown, Towanda	14-2411	3-12-cv-02598
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Hen, Azucena	14-2414	3-12-cv-02771
Sias, Diana Van Pelt	14-2415	3-12-cv-02833
Otto, Harriet	14-2416	3-12-cv-02837
Best, Bettie	14-2417	3-12-cv-02838
Davis, Betty Saki	14-2418	3-12-cv-03017
Roberts, Margaret	14-2419	3-12-cv-03021
Goias, Geraldine	14-2420	3-12-cv-03022
Lona, Lucille	14-2421	3-12-cv-03023
McMurray, Deborah	14-2422	3-12-cv-03025
Doriott, Angelita	14-2423	3-12-cv-03026
Thieman, Donna	14-2424	3-12-cv-03027
White, Claudia	14-2425	3-12-cv-03259
Eshelman, Stephanie	14-2426	3-12-cv-03260
Grillo, Maria	14-2427	3-12-cv-03261
Stefanowski, Lucy	14-2428	3-12-cv-03286
Burghardt, Pamela	14-2429	3-13-cv-07894
Gerber, Marilyn	14-2430	3-12-cv-03326
Tong, Lucy	14-2431	3-12-cv-03328
Venner, Vida	14-2432	3-12-cv-03329
Uslan, Sharon	14-2433	3-12-cv-03330
Goldberg, Ethel	14-2434	3-12-cv-03331
Hudson, Laraine	14-2435	3-12-cv-03335
Rittenhouse, Carolyn	14-2436	3-12-cv-03345
Budd, Randal	14-2437	3-12-cv-03346
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Dykes, Marsha	14-2439	3-12-cv-03348
Foree, Edith	14-2440	3-12-cv-03358
Indich, Terry	14-2441	3-12-cv-3366

Travor, Lois Annette	14-2442	3-12-cv-03399
Steen, Barbara	14-2443	3-12-cv-03429
Charms, Shirley	14-2444	3-12-cv-03511
Denham, Janice	14-2445	3-12-cv-03696
Tanglao, Lourdes	14-2446	3-12-cv-03705
Disosway, Linda	14-2447	3-12-cv-03730
Lare, Sandra	14-2448	3-12-cv-03769
Nealen, Arlene	14-2449	3-12-cv-03770
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Yacoub, Caroline	14-2452	3-12-cv-03795
Baker, Alma	14-2453	3-12-cv-03878
Palma, Lucita	14-2454	3-12-cv-03879
Mateo, Yoshie	14-2455	3-12-cv-03904
Terranova, Patricia	14-2456	3-12-cv-03939
Hill, Mary	14-2457	2-12-cv-03959
Wilson, Selma	14-2458	3-12-cv-04014
Toland Kathleen	14-2459	3-12-cv-04190
Fillippello, Margaret	14-2460	3-12-cv-04423
Harris, Ramona	14-2461	3-12-cv-04424
Lane, Sharon	14-2462	3-12-cv-04426
Whisenant, Louise	14-2463	3-12-cv-04440
Carter, Joan	14-2464	3-12-cv-04453
Glenn, Sue	14-2465	3-12-cv-04454
Sweet, Karen	14-2466	3-12-cv-04566
Hutton, Nancy	14-2467	3-12-cv-04599
Hernandez, Antonia	14-2468	3-12-cv-04601
Favor, Judith	14-2469	3-12-cv-04604
Parker, Esther	14-2471	3-12-cv-04611
Mitchell, Cheryl	14-2472	3-12-cv-04638
Paralikis, Pamela	14-2473	3-12-cv-04656
Bottari, Donna	14-2474	3-12-cv-04663
Hedgepeth, Betty	14-2475	3-12-cv-04664
Sperber, Bernice	14-2476	3-12-cv-04721

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Worthington, Jerrene	14-2478	3-12-cv-04762
Patrina, Chester []	14-2479	3-12-cv-04773
Falcone, Patricia	14-2480	3-12-cv-04802
Anselmo, Victoria	14-2481	3-12-cv-04806
Patterson, Ethel	14-2482	3-12-cv-04836
Haslam, Martha	14-2483	3-12-cv-05018
Julius, Diana	14-2484	3-12-cv-05019
Mott, Leann	14-2485	3-12-cv-05020
Theberge, Jeanne	14-2486	3-12-cv-05060
Walker, Shirley	14-2487	3-12-cv-05085
Bedsworth, Alan []	14-2488	3-12-cv-05094
Crew, Nellie	14-2489	3-12-cv-05108
Astrug, Debra	14-2490	3-12-cv-05205
Dixon, Carolyn	14-2491	3-12-cv-05269
Edgil-Rogers, Judee	14-2492	3-12-cv-05271
Gilmer, Marjorie	14-2493	3-12-cv-05297
Kovalick, Carole	14-2494	3-12-cv-05364
Knutson, Josephine	14-2495	3-12-cv-05383
Smith, Regina	14-2496	3-12-cv-05384
Hamilton-Gamman, S[andra]	14-2497	3-12-cv-05385
Needles, Josephine	14-2498	3-12-cv-05389
Kendrick, Billie	14-2499	3-12-cv-05391
Paxton, Mary	14-2500	3-12-cv-05392
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Knopick, Carol	14-2502	3-12-cv-05485
Osburn, Gaile	14-2503	3-12-cv-05557
Miller, Dolores	14-2504	3-12-cv-05560
Heckard, Shirley	14-2505	3-12-cv-02549
Cline, Diane	14-2506	3-12-cv-05681
Cummings, Sarah	14-2507	3-12-cv-05776
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Collier, Nancy	14-2509	3-12-cv-05978

Sayers, Sheila	14-2510	3-12-cv-05993
Cook, Shirley	14-2511	3-12-cv-06028
Wiegand, Mary	14-2512	3-12-cv-06029
Roland, Annie	14-2513	3-12-cv-06155
Bridgeman, Max	14-2514	3-12-cv-06182
Wong, Anita	14-2515	3-12-cv-06187
Hayden, Jane	14-2516	3-12-cv-06191
McGrath, Sheila	14-2517	3-12-cv-06192
Van Blaricom, Betty	14-2518	3-12-cv-06216
Thomas, Eugune Mid[dleton]	14-2519	3-12-cv-06237
Fuerstnau, Barbara	14-2520	3-12-cv-06264
Halfmann, Mary	14-2521	3-12-cv-06266
Kimizuka, Yoshie	14-2522	3-12-cv-06267
Hofmann, Kathleen	14-2523	3-12-cv-06269
Duggan, Doris	14-2524	3-12-cv-06275
Andorka-Aceves, Deb[orah]	14-2525	3-12-cv-06289
Herndon, Lucy Mae	14-2526	3-12-cv-06301
Delikat, Ellen	14-2527	3-12-cv-06351
Mouser, Donna	14-2528	3-12-cv-06365
Hulsman, Elaine	14-2529	3-12-cv-06366
Kempfer, Faye	14-2530	3-12-cv-06376
Lotter, Dolores	14-2531	3-12-cv-06377
Cummings, Irene Lilli[an]	14-2532	3-12-cv-06378
Irving, Zepher	14-2533	3-12-cv-06397
Marcus, Rita	14-2534	3-12-cv-06430
Halpern, Marion	14-2535	3-12-cv-06432
Ogle, Ann	14-2536	3-12-cv-06433
Bittner, Marcella	14-2537	3-12-cv-06434
Wade, Kay	14-2538	3-12-cv-06437
Ahern, Frances	14-2539	3-12-cv-06439
Boshell, Marsha	14-2540	3-12-cv-06443

Sandt, Faye	14-2541	3-12-cv-06444
Holmes, Leanne	14-2542	3-12-cv-06445
Napoli, Anna	14-2543	3-12-cv-06446
Vaughn, Patricia	14-2544	3-12-cv-06450
Irizarry, Sheila	14-2545	3-12-cv-06451
Kort, Barbara	14-2546	3-12-cv-06453
Kosvick, Melinda	14-2547	3-12-cv-06454
Homa, Barbara	14-2548	3-12-cv-06455
Stepanski, Mary Jo	14-2549	3-12-cv-06456
Lare, Barbara	14-2550	3-12-cv-06457
Nguyen, Susan	14-2551	3-12-cv-06458
Jeet, Lalita	14-2552	3-12-cv-06459
Naik, Khadijah	14-2553	3-12-cv-06460
Bartlett, Ann	14-2554	3-12-cv-06461
Aydin, Jean	14-2555	3-12-cv-06462
Dowd, Jeanette	14-2556	3-12-cv-06463
Van Gosen, Helen	14-2557	3-12-cv-06464
Huddleston, Shirley	14-2558	3-12-cv-06465
Griffin, Jennifer	14-2559	3-12-cv-06466
Crisci, Stephen N. []	14-2560	3-12-cv-06469
Jones, Geraldine	14-2561	3-12-cv-06550
McKinney, Carlene	14-2562	3-12-cv-06711
Karantza, John	14-2563	3-12-cv-06719
Bozue, Dorothy	14-2564	3-12-cv-06770
Cline, Beatrice	14-2565	3-12-cv-06840
Broadstone, Judith	14-2566	3-12-cv-06841
Schmitt, Luise Gerlin[de]	14-2567	3-12-cv-06845
Cherco, Patricia	14-2568	3-12-cv-06846
Neuman, Janet	14-2569	3-12-cv-06850
Isom, Leann	14-2570	3-12-cv-06859
Heiny, Joyce	14-2571	3-12-cv-06860
Vertuccio, Lana	14-2572	3-12-cv-06863
Williams, Susanne	14-2573	3-12-cv-06877

Stevenson, Nada	14-2574	3-12-cv-06899
Elison, Linda	14-2575	3-12-cv-06900
Lingo, Melba	14-2576	3-12-cv-06901
Baylor, Richard	14-2577	3-12-cv-06903
Thompson, Loralee	14-2578	3-12-cv-06905
Miller, Esther	14-2579	3-12-cv-06907
Orr, June	14-2580	3-12-cv-06952
Maki, Gale	14-2581	3-12-cv-06954
Collins, John	14-2582	3-12-cv-06955
McAnulty, Joan	14-2583	3-12-cv-06956
Abney, Virginia	14-2584	3-12-cv-06957
Altson, Amy	14-2585	3-12-cv-07023
Harris, Hope []	14-2586	3-12-cv-07048
Jaeger, Bernadette	14-2587	3-12-cv-07443
Couture, Diane	14-2588	3-12-cv-07819
VanDyke, Patricia	14-2589	3-13-cv-00001
Antoff, Christine	14-2590	3-13-cv-00137
Wyly, Lois Ann	14-2592	3-13-cv-00171
Conner, Cheryl	14-2593	3-13-cv-00442
Kardon, Koula	14-2594	3-13-cv-00718
Bialkowski, Mary	14-2595	3-13-cv-00720
Affronti, Joanne	14-2599	3-13-cv-00816
Bannon, Gladys	14-2600	3-13-cv-00818
Golden, Jane	14-2601	3-13-cv-00894
Pitts, Shirley Ann	14-2602	3-13-cv-00926
Slinkman, William Ric[hard]	14-2603	3-13-cv-00928
Albert, Elizabeth	14-2604	3-13-cv-01062
Hawk, Joycelyn	14-2605	3-13-cv-01063
Pritchard, Helen	14-2606	3-13-cv-01071
Myers, Susan	14-2607	3-13-cv-01215
Brooks, Betty	14-2608	3-13-cv-01314
Hawkins, Amy	14-2609	3-13-cv-01337
Edmondson, Maxine	14-2610	3-13-cv-01340

Kamienski, Mary	14-2611	3-13-cv-01352
Neuman. Delores	14-2612	3-13-cv-01369
Peters. Alohoa	14-2613	3-13-cv-01370
Routhieaux, Marguer[itte]	14-2614	3-13-cv-01371
Alberg, Evelyn	14-2615	3-13-cv-01378
Goodman, Carol Ann	14-2616	3-13-cv-01415
Samuelson. Johann	14-2618	3-13-cv-01476
Rudolph. Joyce	14-2619	3-13-cv-01884
Romeo. Alice	14-2620	3-13-cv-02616
Grems. Mary	14-2621	3-13-cv-02617
McKeon-Cincotta, Le[na]	14-2622	3-13-cv-02649
Jernigan, Mary Lou	14-2623	3-13-cv-02735
Wicker, Marie	14-2624	3-13-cv-02827
Stampliakis. Helen	14-2625	3-13-cv-02836
Crook, Judith	14-2626	3-13-cv-02958
London, Phyllis	14-2627	3-13-cv-03211
Connor. Ruth	14-2628	3-13-cv-03353
Mulqueen. Mary	14-2629	3-13-cv-03353
Bergmann, Ruth	14-2630	3-13-cv-03474
Spallone, Josephine	14-2631	3-13-cv-03741
Maddern, Karen	14-2632	3-13-cv-03929
Marcelles, Sara	14-2634	3-13-cv-04075
Tolston. Betty	14-2635	3-13-cv-05984
Oakes, Miriam	14-2636	3-11-cv-06090
Murphy, Nancy	14-2813	3-12-cv-05082
Montgomery, Rulene	14-3220	3-12-cv-06282
Gaynor, Barbara	14-3267	3-12-cv-01492

APPENDIX C

United States District Court, D. New Jersey.

In re FOSAMAX (ALENDRONATE SODIUM): PRODUCTS LIABILITY LITIGATION.
This Document Relates to: All Actions.

MDL No. 2243.
|
Master Docket No. 08–08(JAP)(LHG).
|
Signed March 26, 2014.

OPINION

PISANO, District Judge.

This matter is presently before the Court on an Order to Show Cause ("OTSC") issued on August 15, 2013 [docket # 2895], directing the Plaintiffs listed in Appendix A of the Order (collectively referred to as "Plaintiffs"), to show cause why their pre-September 14, 2010, injury claims should not be dismissed on preemption grounds pursuant to this Court's ruling in the Bellwether *Glynn* case. *See Glynn v. Merck Sharp & Dohme, Corp.*, Case Nos. 11–503, 08–08, —— F.Supp.2d ——, 2013 WL 3270387 (D.N.J. Jun.27, 2013).

In response to the OTSC, the Court received the following briefs from Plaintiffs: (1) Plaintiff Deborah Thompson's Response to the OTSC [docket # 2931]; (2) Plaintiff Helen Stampliakas's Response to the OTSC [docket # 2932]; (3) Plaintiff Elaine Howe's Response to the OTSC [docket # 17 on 11–6657](4) Plaintiffs' Adverse Reactions and Long–Term–Use Failure–to–Warn Brief ("Adverse Reactions Brief") [docket # 2995(1)]; (5) Plaintiffs' DesignDefect and Other Non Failure to Warn Claims Brief ("Design Defect Brief") [docket # 2995(2)]; (6) Plaintiffs' Procedural Brief [docket # 2995(3)]; and (7) Plaintiffs' Warnings and Precautions Brief [docket # 2995(4)].

Merck replied to Plaintiffs' response to the OTSC and filed the following briefs in support of its position: (1) Reply to Plaintiff Helen Stampliakas's and Plaintiff Deborah Thompson's Responses to the Court's OTSC [docket # 3030]; (2) Reply to Plaintiff Elaine Howe's Response to the Court's OTSC [docket # 3041] (3) Reply to Plaintiffs' Adverse Reactions and Long–Term–Use Failure–to–Warn Brief ("Merck's Adverse Reactions Brief") [docket # 3031]; (4) Reply to Plaintiffs' Design Defect and Other Non–Failure to Warn Claims Brief ("Merck's Design Defect Brief") [docket # 3031(1)]; (5) Reply to Plaintiffs' Procedural Brief [docket # 3031(3)]; and (6) Reply to Plaintiffs' Warnings and Precautions Failure to Warn Brief [docket # 3031(2)].

By way of brief background, Plaintiffs brought this lawsuit against Merck, the manufacturer of Fosamax, which is a drug approved by the United States Food and Drug Administration ("FDA") for the treatment

and prevention of osteoporosis. This matter is part of the multi-district litigation ("MDL") concerning Fosamax and involves allegations that Fosamax causes atypical femur fractures ("A FFs[1]"), it caused Plaintiffs' injuries, and Defendant failed to warn physicians about Fosamax causing AFFs. For the reasons set forth below, Plaintiffs' have failed to show cause why their pre-September 14, 2010, injury claims should not be dismissed on preemption grounds. Preemption was dispositive of *Glynn* and cuts across all pre-label change cases. Accordingly, Defendant is entitled to judgment as a matter of law on the Appendix A Plaintiffs' claims.

I. OVERALL PROCEDURAL HISTORY

In May 2011, the Judicial Panel on Multidistrict Litigation centralized in this Court a number of related actions brought by patients who suffered femur fractures or similar bone injuries after taking Fosamax [docket # 30]. On July 14, 2011, the Court ordered a process for selection of three or four Early Trial Cases and directed a schedule for expert discovery [docket # 113]. On November 14, 2012, the Court designated trial dates for the four Early Trial Cases, with the earliest, *Glynn*, set for April 8, 2013 [docket # 1915]. General fact discovery closed on December 31, 2012, pursuant to Case Management Order No. 10 [docket # 848].

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[1] The abbreviation of atypical femur fracture (singular) is "AFF."

On January 15, 2013, Merck moved for summary judgment in *Glynn* on federal preemption grounds, arguing that the Plaintiffs' claims were preempted because the FDA's rejection of Merck's proposed Precaution disclosing a risk of low-energy femoral shaft fracture from Fosamax use made it impossible for Merck to warn the Plaintiffs' of that risk [docket # 25 in 11–5304]. This Court heard oral argument on the federal preemption issue on March 8, 2013, and reserved decision until a trial record had been established. A jury trial took place in *Glynn* from April 8, 2013 to April 29, 2013. The parties then briefed the preemption issue three more times: a Rule 50(a) motion for judgment as a matter of law at the close of Plaintiffs' case [docket # 198 in 11–5304]; a renewed Rule 50(a) motion at the close of all evidence [docket # 209 in 11–5304]; and a Rule 50(b) renewed motion for judgment as a matter of law [docket # 216 in 11–5304].

On June 27, 2013, after considering all of the parties briefing, evidence, arguments, and the trial record, the Court granted Merck's motion(s) and found that Plaintiff's state law claim for failure to warn was preempted because clear evidence existed that the FDA would not have approved a stronger warning to the Fosamax label as of the date of Ms. *Glynn*'s injury. *Glynn*, 2013 WL 3270387, at * 1. On August 1, 2013, Merck then moved for an OTSC why the claims of all other Plaintiffs with injury dates prior to September 14, 2010, should not be dismissed pursuant to the Court's preemption ruling in *Glynn* [docket # 2857]. On August 5, 2013, Plaintiffs' submitted a letter brief opposing the entry of an OTSC [docket # 2870], and Merck replied by letter on

August 12, 2013 [docket # 2881]. The Court, observing that it had "afford[ed] the Plaintiffs' Steering Committee ... and *Glynn*'s counsel repeated opportunities to present their evidence" and that the *Glynn* ruling turned on issues common to all Plaintiffs, granted Merck's motion on August 15, 2013 [docket # 2895].

As stated above, the parties submitted several briefs and filings in support of their responses to the OTSC. The Court will address each argument separately below.

II. BACKGROUND

A. History of the Fosamax Label Change

In September 1995, the FDA approved Fosamax for the treatment of osteoporosis in postmenopausal women, and in April 1997, the FDA approved Fosamax for the prevention of osteoporosis in postmenopausal women. Since this time, Fosamax has remained FDA approved for the treatment and prevention of postmenopausal osteoporosis. On June 13, 2008, the FDA contacted Defendant and other bisphosphonate[2] manufacturers and requested any investigations they conducted "regarding the occurrence of atypical fractures with bisphosphonate use," any investigational plans, and "all hip and femoral fracture case reports" they received [docket # 3032, *Merck's Preliminary Statement of Facts Relating to the Court's Order to Show Cause*

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[2] Fosamax belongs to a class of drugs known as bisphosphonates.

("Merck's Statement of Facts") ¶ 28]. The FDA also asked that Defendant and the other bisphosphonate manufacturers make an effort where possible "to clarify the fracture location and the duration of bisphosphonate exposure for all case reports." *Id.* at ¶ 44. The FDA explained that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates" and was "concerned about this developing safety signal." *Id.* at ¶ 43.

On July 18, 2008, Defendant responded to the FDA's request and included summary tables of clinical and post-marketing data, clinical Council for International Organizations of Medical Sciences ("CIOMS") reports, and post-marketing CIOMS reports. *Id.* at ¶ 47. The FDA's review of this data as well as the data from other bisphosphonate manufacturers "did not show an increase in ... [the risk of atypical subtrochanteric femur fractures] in women using these medications." [docket # 3035, *Declaration of Karen A Confoy in Support of Merck's Replies to Plaintiffs' Briefs in Response to Court's Order to Show Cause and in Support of Merck's Preliminary Statement of Facts* ("Confoy Dec."), Ex. 73].

On September 15, 2008, Defendant submitted a Prior Approval Supplement ("PAS") to the FDA, proposing "to add language to both the Precaution[s] and Adverse Reactions/PostMarketing Experience section[s] of the label to describe low-energy" subtrochanteric femoral fractures. Merck's Statement of Facts, ¶ 73. Defendant explained that "[i]t is not possible with the present data to establish

whether treatment with" Fosamax "increases the risk of [these] ... low-energy subtrochanteric and/or proximal shaft fractures," but because there is a temporal association between these fractures and Fosamax, Defendant thought that it was "important to include an appropriate statement about them in the product label." *Id.* Defendant sought to add the following language to the Precautions section of the label:

> Low–Energy Femoral Shaft Fracture
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonatetreated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e .g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopaedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation

> of the patient, based on individual benefit/risk assessment.
>
> [*Id.* at ¶ 74].

Additionally, Defendant proposed adding "low-energy femoral shaft fracture" to the Adverse Reactions/Post–Marketing Experience section of the label and the following statement to the Patient Package Insert: "Patients have experienced fracture in a specific part of the thigh bone. Call your doctor if you develop new or unusual pain in the hip or thigh." *Id.*

On April 15, 2009, an FDA representative e-mailed Defendant and stated that the label change to the Adverse Reactions/Post–Marketing Experience section of the label would be approved but the label change to the Precautions section would not be approved. *Id.* at ¶ 79. On May 22, 2009, the FDA formally responded to Defendant's proposed label change, recommending that it add "low energy femoral shaft and subtrochanteric fractures" to the Adverse Reactions/Post–Marketing Experience section of the label; however, the FDA still did not approve the label change to the Precautions section. *Id.* at ¶ 80. Moreover, the FDA warned that Fosamax "may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if [it is] ... marketed with" these label changes "before [FDA] approval...." *Id.*

On July 2, 2009, Defendant submitted to the FDA a Changes Being Effected ("CBE") supplement to add the FDA's proposed language about femur fractures to the Adverse Reactions/Post–Marketing Experience section of the label, which was later approved. *Id.* at

81. On March 10, 2010, the FDA issued a Drug Safety Communication, in which it stated that "[a]t this point, the data that FDA has reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures" *Merck's Statement of Facts*, $ 85. The FDA did state, however, that it was "working closely with outside experts, including members of the ... American Society of Bone and Mineral Research Subtrochanteric Femoral Fracture Task Force, to gather additional information that may provide more insight into this issue." *Id.*

On September 14, 2010, the American Society for Bone and Mineral Research ("ASBMR") published an article entitled *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research. Id* . at ¶ 86. The report stated that although there is an association between long-term bisphosphonate use and A FFs, the association had not been proven to be causal. *Id.* The FDA responded to the report by issuing a Drug Safety Communication, in which it stated "[a]lthough it is not clear if bisphosphonates are the cause [of AFFs], these unusual femur fractures have been identified in patients taking these drugs." *Id.* at $ 87. Regarding the ASBMR Task Force's recommendation of a label change, the FDA stated that it "has assembled and is thoroughly reviewing all long term data available on the products, as well as all safety reports ..." and would be "considering label revisions." *Id.* (emphasis added).

In October 2010, the FDA issued another Drug Safety Communication, informing that it would require all bisphosphonate manufacturers to add information on AFFs to the Precautions section of the drug labels and require a new Limitations of Use statement in the Indications and Usage section of the label because "these atypical fractures may be related to long-term ... bisphosphonate use." *Id.* at ¶¶ 88–89. It reiterated that it was still "not clear if bisphosphonates are the cause," but noted that these "unusual femur fractures" may be related to long-term bisphosphonate use. *Id.* at $ 88. The FDA's proposed labeling language noted that "[c]ausality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates." *Id.* at ¶ 89. On January 11, 2011, Defendant submitted the agreed upon label changes to the FDA. *Id.*

Currently, the Fosamax label includes the following language: "Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients.... Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates. Atypical femur fractures most commonly occur with minimal or no trauma to the affected area." [docket # 2996, *Declaration of Donald A. Ecklund* ("Ecklund Dec."), Ex. 9].

B. *Glynn* Ruling

As noted above, before the Court in *Glynn* were several motions by Defendant[3] , all of which were premised on federal preemption. The issue in these motions was whether clear evidence existed that the FDA would not have approved a stronger warning to the Fosamax label, thereby warranting preemption of the *Glynn* Plaintiffs' failure to warn claim. *See Wyeth v. Levine*, 555 U.S. 555, 129 S.Ct. 1187, 173 L.Ed.2d 51 (2009). This Court heard oral argument on the preemption issue on March 8, 2013, and reserved decision until a trial record had been established. *See* Fed.R.Civ.P. 78. A jury trial took place from April 8, 2013 to April 29, 2013, and the jury returned a verdict for Defendant, finding that Plaintiff *Glynn* did not prove that she experienced an AFF in April 2009 by a preponderance of the evidence.

On the day following the conclusion of the trial, the Court held an in-person status conference where it discussed the preemption issue and gave the Plaintiffs twenty-one (21) days to submit "proposed fact findings that [were] based upon the record in opposition to" the preemption motions. [docket # 250

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[3] The motions before the Court in *Glynn* were: (1) Defendant's Motion for Summary Judgment based upon Federal Preemption [docket # 25 in 11–5304]; (2) Defendant's Motion for Judgment as a Matter of Law pursuant to Rule 50(a) [docket # 198 in 11–5304]; (3) Defendant's Renewed Motion for Judgment as a Matter of Law pursuant to Rule 50(a) [docket # 209 in 11–5304]; and (4) Defendant's Renewed Motion for Judgment as a Matter of Law pursuant to Rule 50(b) [docket # 216 in 11–5304].

in 11–5304, *Hearing Tr.*, 19:24–20:1; April 30, 2013]. Thereafter, on May 6, 2013, Defendant submitted its Renewed Motion for Judgment as a Matter of Law pursuant to Rule 50(b) [docket # 216 in 11–5304], arguing that the *Glynn* Plaintiffs' claims were preempted because Defendant submitted to the FDA all of the information relevant to a label change and tried to change the Precautions section of the label to include low-energy femoral fractures, but the FDA rejected this change. The Court agreed with Merck's position and on June 27, 2013, granted Defendant's motion(s). *See* Generally *Glynn*, 2013 WL 3270387.

C. Arriving at the OTSC

With the history of *Glynn* as a backdrop, it is necessary to address the evolution of the preemption issue, how the case has gotten to the point of having an OTSC on the issue, and the fact that the parties have been aware of the potential global effects preemption could have on the entire MDL for at least two (2) years. Throughout the entire pre-trial, trial, and post-trial proceedings in *Glynn*, the Court made it clear that, prior to ruling on preemption, it wanted the parties to introduce any and all relevant evidence to the issue because of the effects it could have on the MDL as a whole. During this time—even prior to any motions being filed by Defendant—Plaintiffs' were aware of the exact position that Merck took surrounding preemption, how Merck planned to raise this argument, and the fact that Merck believed preemption likely hinged on the date of a Plaintiff's injury.

Indeed, before Ms. *Glynn* was even selected as the Bellwether case for trial, the parties appeared before

the Court on May 14, 2012, where counsel for Merck reiterated the fact that the date of injury was central to the analysis and advised the Court and Plaintiffs of Defendant's position on preemption. [docket # 1397, *Hearing Tr.*, 13:25–14:2; 14:12–14:14; 15:16–15:19; 22:5–22:7; May 14, 2012 ("MR. MARSHALL: ... I want to focus in on some of the labeling issues because they're going to be very important in the case ... [it's] going to be a very important point in these cases because we will be raising a preemption argument ... [t]hat defense will be raised as a substantive legal motion ... [and] it will be based upon when the injury occurred ... [a] key factor ... is the timing of the injury....")]. Stated differently, for almost an entire year prior to the *Glynn* trial, Plaintiffs were aware of Defendant's position on preemption, the fact that it would be raised by way of substantive motion and that such motion would be directly related to the timing of injury. Fact discovery closed seven (7) months thereafter and the preemption issue was then briefed four separate times.

As the *Glynn* trial moved closer, the parties were advised of the Court's desire to have any and all arguments and evidence relevant to preemption on the record. [docket # 244 in 11–5304, *Trial Tr., Vol. 9*, 1885:7–1885:12; April 22, 2013 ("THE COURT: ... I have indicated my intention to ultimately rule on that [preemption] motion after I've had the benefit of a complete trial record ... I think I'm correct that a full trial record would benefit me and both sides before a ruling is made.")]. Further, after the close of Plaintiff's case in the *Glynn* trial, Plaintiffs were *again* made aware of the exact position Merck took

with respect to the evidence set forth and the issues Merck planned to *again* raise surrounding preemption. *Id.* at 1908:12— 1908:17 ("MR. MARSHALL: ... The FDA had in its possession all of the information that plaintiffs now rely upon to say that a label change could be made. We tried to do it, it was rejected. We are precluded, prevented from doing it. That, your Honor, is the preemption argument."). Despite Merck's contention that no dispute of fact existed for the jury to decide, the Court continued to reserve its decision on the preemption motion(s) to ensure a full trial record was established with all evidence relevant to the issue.

Immediately following the trial on April 30, 2013, the parties appeared before the Court to discuss the process of moving the MDL forward and, again, the Court reiterated that it has been urging Plaintiffs to come forward with *any and all evidence* on the preemption issue, as the parties all agreed that it would have widespread implications on the M DL as a whole:

> *MR SEEGER:* ... **I'm thinking that the preemption issue because it's going to cut across all 3,000 cases. Pretty much if it goes the wrong way for plaintiffs, it's pretty much the end of the litigation.**
>
> ...
>
> *THE COURT*: There have been three iterations of the preemption motion and **my position all along was to make f that I wanted to be sure, first of all, that I had a complete record from which to decide the preemption issue**. And I thought the best way to do that was to try the *Glynn* case,

because that was the case that was coming in, knowing that there was going to be **evidence introduced which would bear upon Merck's conduct with the FDA and whether there would be clear evidence that [the] FDA would not have permitted the label change**, which is what Merck has to show under *Wyeth v. Levine*.

...

I don't know what more you want to put in the record. **I invited you, I invited the plaintiffs and I was urging the plaintiffs to put in what there could be bearing on the question.** I don't know what else there is.

...

The issue in the case is whether there's anything in the regulatory record from which the Court would conclude that it's clear the FDA would not have permitted the label change. Now, the label change was an issue in the *Glynn* case. It was an issue in the *Glynn* case that was addressed by Dr. Blume, it was addressed by Dr. Madigan and it certainly was addressed by Dr. Santora and Daifotis.

I'm not so sure there's anything else and if there was something else, I have been begging for it.

...

... **It was clear to me and everybody else that there was substantial consequences to this motion. We've had a hundred conversations, all of us, since then where I have been saying the same thing, namely, that I wanted-that it was**

important to decide this case, this issue one way or another so that there could be some appellate review and we get a sense of it, because we know we're holding 3300 cases hostage.

[docket # 250 in 11–5304, *Hearing Tr.*, 5:10–5:13; 6:10– 6:19; 7:13–7:17; 16:6–16:14; 18:15–18:21; April 30, 2013 (emphasis supplied)].

Similarly, after the Court granted Merck's preemption motion(s) in *Glynn*, the parties appeared before the Court on July 18, 2013, to again address, among other things, how the preemption issue would be treated going forward and the fact that preemption would cut across all of the cases in the MD L:

> *THE COURT:* I think it's an accurate statement, Mr. Morris, that **I have been consistent in asking the plaintiffs to come forward with any evidence that would bear upon that preemption decision and I didn't decide it until I was satisfied that there had been a full opportunity to be heard on the question and the opinion stands for itself.**
>
> ...
>
> This business about all the plaintiffs having their own claims and their own injuries and their own doctors is all very well and fine and that's true, **but the focus from the preemption issue, the focus is more on Merck than on the plaintiffs.**
>
> *THE COURT:* ... [W]hat I would expect then is there to be some sort of an effort by Merck to close the door on these cases.

MR. MORRIS: **Right, we expected that ...**

[docket # 2998, *Hearing Tr.*, 10:3–10:8; 10:16–10:20; 11:8–11:10; July 18, 2013 (emphasis supplied)].

As a review of the record reveals, the preemption issue has existed since this MDL's inception and preemption has almost certainly been the forefront of the litigation for the past two (2) years. It has never been a secret as to what Merck's position is with respect to preemption, and Plaintiffs have long been aware that their case(s) may depend entirely on the date of injury. Further, as referenced above, for the past two (2) years the parties and the Court have been operating under the common understanding that this Court's decision on preemption could impact the entire MDL. Stated differently, Plaintiffs and Defendant knew that while the motions before the Court in *Glynn* were specific to the date of Ms. *Glynn*'s injury, the Court's decision on such motions would almost certainly have an effect on a substantial amount of Plaintiffs other than Ms. *Glynn*. Thus, the Court purposely reserved deciding the issue to ensure that *any and all facts relevant to preemption* would appear on the record. In doing so, the Court repeatedly urged Plaintiffs to come forward with all evidence bearing on preemption, allowed the parties several opportunities to brief the issue, entertained oral argument on the motion(s), conducted an entire trial which invited any evidence relevant to preemption, and addressed the issue at various hearings. Then, after finally ruling on preemption in *Glynn*, the Court issued an OTSC—giving the parties yet another opportunity to brief the issue—to address what has *long* been known as a

predominant issue in the case: namely, what effect does the Court's preemption ruling have on the other Plaintiffs whose injuries occurred prior to the date of the label change?

III. DISCUSSION

A. Procedural Arguments

The parties each submitted briefing on the procedural aspects of the Court's OTSC in the context of an MDL. Plaintiffs' and Defendant concede that Rule 56 provides the proper standard for the Court's analysis here; however, the parties disagree over the burden shifting, as well as the Court's ability to utilize an OTSC to apply the *Glynn* ruling to other Plaintiffs. This Court agrees with the parties' contention that Rule 56 provides the exclusive mechanism by which the Court can resolve the dispositive issues presented by Merck's preemption defense before trial(s).

i. Procedural Analysis

The Court must first address the proper standard to be applied pursuant to Rule 56 as well as where the appropriate burden lies in this OTSC context. Under Rule 56, summary judgment is applicable when the Court is satisfied that there is no genuine issue of material fact and the evidence establishes the moving party's entitlement to judgment as a matter of law. *See Celotex Corp. v. Catrett*, 477 U.S. 317, 323, 106 S.Ct. 2548, 2553, 91 L.Ed.2d 265 (1986). "If the moving party meets the initial burden of establishing that there is no genuine issue, the burden shifts to the nonmoving party to produce

evidence of a genuine issue for trial." *Degrange v. W.*, 196 F. App'x 91, 93 (3d Cir.2006).

This Court agrees with Merck's contention that Defendant's initial burden pursuant to Rule 56 has already been met by way of the briefing in *Glynn*. As stated above, Merck briefed the preemption issue four (4) separate times and in doing so, met its burden of establishing that there is no genuine issue(s) of fact with respect to preemption. This is further evidenced by the Court's judgment as a matter of law in favor of Merck, holding that clear evidence exists that the FDA would not have approved a stronger warning prior to the date of Ms. *Glynn*'s injury.[4] *See* Generally *Glynn*, 2013 WL

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[4] It should be noted, however, that despite the *Glynn* ruling being specific to Ms. *Glynn* and the date of her injury, Merck's briefing in *Glynn* is still relevant to all Plaintiffs' identified in this Court's OTSC because the briefs in *Glynn* centered generally on *when* clear evidence existed that the FDA would not have approved a label change. *See Defendant Merck Sharp & Dohme Corp.'s Memorandum of Law in Support of Motion for Summary Judgment Based upon Federal Preemption*, p. 18 [docket # 25 in 11–5304] ("... [I]t was not until the ASBMR report was issued in September 2010, reporting that bisphosphonates, when used long-term, may be related to femoral fractures, that the FDA determined available scientific evidence supported a Precaution."); *Defendant Merck Sharp & Dohme Corp.'s Memorandum of Law in Support of its Motion for Judgment as a Matter of Law*, p. 2, 18 [docket # 198 in 11–5304] and *Defendant Merck Sharp & Dohme Corp.'s Memorandum of Law in Support of its Renewed Motion for Judgment as a Matter of Law*, p. 1, 12 [docket # 209 in 11–5304] ("[Plaintiff's] claims would be preempted because Merck proposed ... such a Precaution and the FDA rejected it ... such a rejection is "clear evidence" that the FDA would have

3270387. Thus, Merck has demonstrated the absence of any genuine issue of material fact surrounding preemption and the burden is therefore shifted to Plaintiffs to produce a genuine issue for trial by way of their briefing in response to the Court's OTSC.

Plaintiffs' assert that they have met this burden because subsequent to the *Glynn* ruling, there have been additional documents exchanged and additional expert testimony which creates a genuine issue of fact as to what Merck could have or should have done in connection with updating its label.[5] However, what

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rejected any warning about fractures ..." and "Dr. Blume testified clearly and repeatedly ... that a pharmaceutical company's duty to change its label to warn of an adverse event does not arise until there is 'reasonable evidence of a causal association' under 21 C.F.R. § 201.57"); *Merck Sharp & Dohme Corp.'s Reply in Support of Rule 50(B) Motion for Judgment as a Matter of Law*, pp. 5–6 [docket # 230 in 11–5304] ("Simply put: the change in the FDA's approach between 2008 and 2010 did not result from a change in FDA policy with respect to line-editing proposed warnings ... Rather, it resulted from an evolution in the FDA's views about the science relating to atypical femur fractures, which did not crystallize until late 2010.").

[5] Plaintiffs' claim that "new evidence" presently before the Court includes Ex. 161 to the *Declaration of Donald A. Ecklund*, which was a statement from the FDA in December, 2010 about why it was rejecting the label change and that because the FDA struck out the term "stress fracture," this Court cannot find that clear evidence exists that the FDA would have rejected a label change that did not use the "stress fracture" language. However, it should be noted that the December, 2010 statement from the FDA was before the Court in *Glynn* and therefore, this is not "new evidence" that the Court has not already considered in determining that no material fact dispute exists. *See Declaration of Edward*

Merck *could have* or *should have* done is immaterial because we know what Merck *did*. Similarly, ***Wyeth v. Levine*** provides for preemption where there is clear evidence that the FDA *would have* rejected a label change, and again, we know that the FDA *did* reject it. Thus, any expert testimony relating to what Merck *could have* or *should have* done, and what the FDA *would have* done in response to the same, is purely speculation and does not rise to the level of being a genuine fact dispute. Allowing Plaintiffs the opportunity to present individual expert testimony would also defeat the efficiency of an MDL because Plaintiffs would go through expert after expert, and none of the testimony would change what actually transpired between Merck and the FDA.

Further, the Court disagrees with Plaintiffs' contention that their Seventh Amendment rights and the procedural protections safeguarded in Rule 56 are being circumvented. Plaintiffs' suggest that the preemption determination must be made by a fact finder; however, if this were the case, the Court's preemption ruling in *Glynn* would be improper.[6] This assertion is not convincing. Rather, as evidenced by the cases cited to by Plaintiffs, where there is *no factual dispute* surrounding a preemption determination, summary judgment is proper. *See Boyle v. United Technologies Corp.*, 487 U.S. 500, 501, 108 S.Ct. 2510, 2513, 101 L.Ed.2d 442 (1988) ("If

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Braniff in Support of Plaintiff's Opposition to Defendant's Motion for Judgment as a Matter of Law, at Ex. 1 [docket # 199 to 11–5304].

[6] It should be noted that Plaintiff *Glynn* did not appeal this Court's June 27, 2013, Order on preemption.

the evidence presented in the first trial would not suffice, as a matter of law, to support a jury verdict under the properly formulated [preemption] defense, *judgment could properly be entered for respondent at once*, without a new trial. It is unclear from the Court[s] of Appeals' opinion, however, whether it was in fact *deciding that no reasonable jury could*, under the properly formulated [preemption] defense, have found the petitioner on the facts presented, or rather was assessing on its own whether the defense had been established. *The latter would be error*, since whether the facts established the conditions for the [preemption] defense is a question for the jury." (emphasis supplied)); *Brown v. Earthboard Sports USA, Inc.*, 481 F.3d 901, 913 (6th Ci r.2007) ("*Should the movants fail to meet their burden* ... such as *if a genuine issue of material fact exists* regarding the claim's actual qualification for federal preemption, the matter must be determined by the factfinder." (emphasis supplied)).

Plaintiffs' procedural protections and Seventh Amendment argument is no more than a reiteration of the summary judgment standard. As the Court has already stated, Merck met its burden of proving that no there is no genuine issue of fact surrounding preemption by way of the briefing and trial record developed in *Glynn*. As a result, Plaintiffs are being afforded the procedural protections of Rule 56, and this Court is neither violating their Seventh Amendment rights nor "deciding factual disputes." Were the Court to determine that there *is* a genuine dispute of fact, it would deny summary judgment; however, in determining that there *is no factual*

dispute, the Court is not thereby "deciding factual disputes."

Moreover, utilizing an OTSC to apply a prior legal ruling to other Plaintiffs in an M D L is hardly inappropriate as suggested by Plaintiffs. Rather, several M DL courts have used an OTSC to do just that. *See In re Darvocet, Darvon & Propoxyphene Products Liab. Litig.*, 2012 WL 3290145, at * 1 and fn. 1 (E.D.Ky. Aug. 10, 2012) ("Here, the Court has previously determined that product liability claims against Generic Defendants are preempted ... [The Show Cause Order] directed all plaintiffs with claims against any Generic Defendant to show cause why those claims should not be dismissed pursuant to the Court's Memorandum Opinion and Order Regarding Generic Defendants' Motions to Dismiss."); *In re Allstate Ins. Co. Fair Labor Standards Act Litig.*, 2009 WL 3011042, at * 1 (D.Ariz. Sept.16, 2009) ("[I]n this MDL action ... summary judgment would be granted in the defendants' favor as to all claims of any Continuing Plaintiff who did not show cause in writing ... explaining why the Court's reasoning in the summary judgment order ... which the Court entered in the ... member case, should not be applied to him or her."); *In re Sulzer Hip Prosthesis & Knee Prosthesis Liab. Litig.*, 455 F.Supp.2d 709, 712–13 (N.D.Ohio 2006) ("In *Moore*, Sulzer moved for summary judgment on the ground that all of Moore's claims were preempted by federal law ... In light of the Court's conclusion in *Moore*, Sulzer moved the Court to issue an Order requiring all similarly-situated plaintiffs ... to show cause why their cases should not also be dismissed. The Court acquiesced to this request."). In doing so, the Court is not

applying a *factual* determination made in *Glynn* to the Plaintiffs identified in the OTSC, but a *legal* determination: namely, that there is clear evidence the FDA would have rejected a stronger Fosamax warning label, thereby preempting Plaintiffs' claims.

Further, the OTSC does not give an impermissible preclusive effect to the *Glynn* ruling because the Court is not automatically applying the holding in *Glynn* to other Plaintiffs. Instead, despite having been aware of the preemption issue for two (2) years, briefing the issue four (4) separate times, and conducting an entire trial whereby any evidence relevant to preemption could be introduced, the OTSC provides affected Plaintiffs *another* opportunity to identify genuine issues of material fact that would preclude summary judgment on their claims. Plaintiffs' failure to meet their burden pursuant to Rule 56 does not then equate to issue and/or claim preclusion. Plaintiffs' contention that further factual and expert discovery should be afforded these Plaintiffs, and that each MD L Plaintiff is entitled to litigate the preemption issue, is similarly misguided. The Court has repeatedly advised Plaintiffs' counsel to come forward with any and all evidence surrounding preemption; thus, the failure to properly gather factual and expert discovery prior to this OTSC is no fault other than Plaintiffs. Additionally, in making these discovery related arguments, Plaintiffs are improperly focusing on the relationship between the *individual Plaintiffs* and *Merck*; however, as the Court has explicitly stated on the record, the preemption analysis is entirely dependent on the relationship between *Merck* and the *FDA*.

The Court is not convinced that, whether clear evidence exists that the FDA would have rejected a stronger warning label to Fosamax, has any relevance to the individual Plaintiff and his or her potential factual differences. Rather, the material fact relevant to the preemption determination and the OTSC does not differ amongst the Plaintiffs listed in Appendix A—an injury that occurred prior to September 14, 2010. Plaintiffs have failed to show how uncovering additional information on behalf of each individual Plaintiff would change the analysis or preclude summary judgment here and therefore an extension of discovery is not warranted. *See Penn. Dep't of Pub. Welfare v. Sebelius*, 674 F.3d 139, 157 (3d Cir.2012). Further, while the Court is sympathetic to the Plaintiffs and their respective injuries, to give each of the Plaintiffs identified in the Courts OTSC their "own day in court" to litigate a legal issue that has already been conclusively determined would not only be a waste of judicial resources but would be contradictory to the premise of pre-trial motions and summary judgment. While Ms. *Glynn* had her "day in court," such was for the purpose of developing a complete trial record on the preemption issue; however, the Court need not have several hundred trial records, with the same evidence, to decide the very same issue.

As Merck correctly points out, this case is distinguishable from *In re TMI Litig.*, 193 F.3d 613 (3d Ci r.1999) *amended*, 199 F.3d 158 (3d Ci r.2000) because there, the Third Circuit concluded that the District Court "could not properly extinguish the substantive rights of the 1,900 Non–Trial Plaintiffs *merely because* all of the cases had been consolidated

... because the Non–Trial Plaintiffs were not even litigating their claims and not presenting arguments to the District Court." *Id.* at 725 (emphasis supplied). Here, the Court is not merely applying its ruling in *Glynn* to Plaintiffs, but has repeatedly urged Plaintiffs to come forward with evidence as to why their claims are not preempted, is giving Plaintiffs another opportunity in the context of the OTSC to present arguments to the Court as to why their claims are not preempted, and is applying the Rule 56 standard in doing so.

The Court has consistently made clear that it expected Plaintiffs to present all of the pertinent evidence on the issue of preemption by the end of the *Glynn* trial. Thus, Plaintiffs' argument that they have been denied the opportunity to develop expert testimony relevant to the preemption issue is ill-advised. The Court is also satisfied that additional individualized factual discovery is unnecessary because the crux of the preemption inquiry focuses on the relationship between Merck and the FDA, and has nothing to do with the facts or injuries of the individual Plaintiffs.[7] Stated differently, facts relating to *each individual Plaintiff* will not have any effect on whether *Merck* had a duty to warn, and testimony from individual experts regarding what Merck and the FDA *could* or *would* have done will not change what Merck and the FDA *did*.

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[7] Individualized discovery may be appropriate if the parties were disputing *causation* such as the Plaintiffs in *TMI*; however, the preemption analysis here is dependent on whether *Merck* had a state law *duty* to update its warning label.

Accordingly, the Court finds that utilizing an OTSC to apply the *Glynn* ruling to those Plaintiffs' whose injuries occurred prior to September 14, 2010, without allowing additional discovery is not improper.

B. Design Defect and Other Non–Failure to Warn Claim Arguments

The parties each submitted briefing with respect to whether the Court should utilize the OTSC to apply the *Glynn* preemption ruling to Plaintiffs' design defect and other non-failure to warn claims. In support of their position, Plaintiffs' argue that the Court's preemption ruling in *Glynn* only applied to a state law failure to warn claim and therefore did not address, and cannot be applied to, state law claims for design defect, negligence, fraud, breach of warranties, consumer protection/deceptive trade practices, and unjust enrichment. Specifically, Plaintiffs' argue that these claims do not "emanate from a general theory that Merck failed to provide an adequate warning about the risk of atypical femur fractures" and therefore, Defendant has not met its Rule 56 burden to obtain summary judgment on these claims. *See Plaintiffs' Design Defect Brief*, at p. 8.

i. Design Defect and Other Non–Failure to Warn Claim Analysis

As discussed in the procedural analysis, Merck's Rule 56 burden surrounding preemption was met by way of the briefing in *Glynn*. Plaintiffs' contention that applying the *Glynn* ruling to design defect and other non-failure to warn claims would improperly relieve Merck of its burden to show that it is entitled

to judgment on such claims is, in the abstract, persuasive. Importantly, however, Plaintiffs' design defect and other non-failure to warn claims are based entirely on the premise that Fosamax had risks which should have been disclosed to consumers. Thus, these claims rise and fall with a claim for failure to warn and utilizing an OTSC to preempt Plaintiffs' design defect and other non-failure to warn claims based on this Court's ruling in *Glynn* is not improper. *See Cooper v. Bristol–Myers Squibb Co.*, 2013 WL 85291, at *9 (D.N.J. Jan. 7, 2013) ("Therefore, having already determined that Plaintiff is unable to establish any triable issue with respect to his failure-to-warn claim, Plaintiff's design claim correspondingly fails."); *Begley v. Bristol–Myers Squibb Co.*, 2013 WL 144177, at * 9 (D.N.J. Jan. 11, 2013) ("... [A] product bearing an adequate warning is not in [a] defective condition, nor is it unreasonably dangerous ... Hence, Plaintiff's defective design claim fails because she has not demonstrated that the [product's] warning was inadequate." (internal citations omitted)); *Stafford v. Wyeth*, 411 F.Supp.2d 1318, 1320 (W.D.Okla.2006) (granting summary judgment to Defendant where plaintiff failed to establish that Defendant's failure to warn was the proximate cause of her injury and plaintiff's non-failure to warn claims, including negligence and design defect, "all hinge on defendant's alleged failure to warn."); *Chatman v. Pfizer, Inc.*, 2013 WL 1305506, at * 4 (S.D.Miss. Mar.28, 2013) ("... [T] he national consensus is that [plaintiff's] other claims are poorly camouflaged failureto-warn claims, and therefore most courts have rebuffed plaintiffs' attempts to recover under alternative state-law

theories of liability including negligence and fraud ... If [plaintiff's] remaining claims are disguised failure-to-warn claims, then they are unquestionably subject to [the failure to warn] preemption analysis" ... Further, "[t]here can be no doubt that [plaintiff's design defect] claims are [also] based on the inadequacy of the warning she was given, and therefore these claims are subject to [preemption] ..." (internal citation omitted)).

Plaintiffs' contend that neither their negligent design defect nor strict liability design defect claims sound in failure to warn, but that fact questions exist as to whether Fosamax was unreasonably dangerous, or whether Merck was negligent in failing to conduct adequate testing and use due care in the design and manufacture of Fosamax. In support of this argument, however, Plaintiffs' advance only a summary of the law and tests that may be applied to determine if a product is defectively designed but offer no law as to which test applies here and no facts and/or evidence to show that Fosamax was in fact defectively designed or that Merck acted negligently. Further, aside from the pleadings, this appears to be the first time in a six (6) year-long litigation, after a two (2) year focus on preemption, discovery, numerous briefs on the preemption issue and an entire trial worth of evidence, that Plaintiffs' believe Fosamax was defectively designed or that Merck was negligent in conducting testing of the drug. The entire MDL has centered on Merck's conduct in failing to update Fosamax's warning label.

To this end, Plaintiffs' make a conclusory statement that their complaints have "typically

alleged" facts in support of their non-failure to warn, strict liability and negligence based design defect claims, but offer no facts as to which, or how many Plaintiffs have in fact pled such claims. Plaintiffs' are conflating the standard to withstand a Federal Rule of Civil Procedure 12(b)(6) motion to dismiss with the standard to be applied here, which is that of a Rule 56 motion for summary judgment. Surely, Plaintiffs general description of what some complaints "typically allege" may constitute plain statements showing that Plaintiffs are entitled to relief, *see Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 557, 127 S.Ct. 1955, 167 L.Ed.2d 929 (2007); however, meeting the threshold requirement of Rule 12(b)(6) is hardly sufficient to defeat Merck's showing that it is entitled to judgment as a matter of law on preemption grounds.

Indeed, Merck has met this burden. Plaintiffs' design defect and other non-failure to warn claims are merely disguised failure to warn causes of action, which is evidenced by the pleadings that Plaintiffs attach as exhibits in response to the OTSC and the fact that the entire litigation, focus of the parties' discovery, and evidence put before the Court has been based entirely on Fosamax's warning. In fact, one of the complaints cited to by Plaintiffs in support of the argument that the design defect claims are independent of the warning specifically states that "Fosamax, as researched, tested, developed, designed, licensed, manufactured, packaged, labeled, distributed, sold and marketed by Defendant *was defective due to inadequate warnings and instructions.*" *See* [docket # 2996, *Ecklund Dec.*, Ex. 167 at ¶ 97 (emphasis supplied)]. Plaintiffs have not

alleged that Fosamax's chemical composition could have been changed, but rather, that the product was unreasonably dangerous because it was not accompanied by a proper warning. Similarly, Plaintiffs' negligent design defect claims allege that Merck failed to properly test the drug, and had Merck exercised due care in testing the product, Fosamax's label would have been updated sooner. Again, however, these contentions are nothing more than speculation and while Plaintiffs' design defect and other non-failure to warn arguments begin by focusing on the product and/or Merck's conduct on the front end, they conclude by focusing on how the consequence—the label—*may* have been different as a result. *See Estate of Popolizio v. Ford Motor Co.*, 2013 U.S. Dist. LEXIS 79361, at *5–6, 2013 WL 2459878 (D.N.J. June 5, 2013) ("the non-moving party cannot rely on unsupported assertions, bare allegations, or speculation to defeat summary judgment.").

The Court also disagrees with Plaintiffs' contention that state law design defect claims cannot be preempted under the federal Food, Drug, and Cosmetic Act ("FDCA"). Plaintiffs make this assertion by stating that every Federal Circuit Court to address whether the FDCA preempts design defect claims has found no preemption; however, instead of providing the Court with an analysis of how, or if, the cases are even applicable to the facts here, Plaintiffs merely list the case names and citations. As Merck correctly points out, the cases cited to by Plaintiffs are distinguishable from the instant matter and

therefore, carry little weight with respect to whether Plaintiffs' design defect claims can be preempted.[8]

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[8] In *Desiano v. Warner–Lambert & Co.*, 467 F.3d 85 (2d Cir.2006), the Second Circuit held that because Plaintiff's state law causes of action merely required *some* proof of fraud on the FDA but such proof was not conclusive, the Supreme Court's holding in *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 121 S.Ct. 1012, 148 L.Ed.2d 854 (2001) that all fraud on the FDA claims are preempted did not apply to *automatically* preempt Plaintiff's state law claims which only incidentally involved fraud. The Court in *Desiano* did note that state based tort liability falls within a state legislature's prerogative to regulate matters of health and safety and therefore, a presumption against preemption should apply; however, the Court went on to state that "there may be reasons to override that presumption [against preemption]." *See Desiano*, 467 F.3d at 94. Here, however, the Court is not applying preemption based on a fraud on the FDA theory to *automatically* preempt Plaintiffs' remaining claims that *incidentally* relate to fraud but rather, after giving Plaintiffs' an opportunity to be heard, is applying preemption based on a failure to warn ruling to preempt Plaintiffs' remaining claims that are based entirely on this same theory.

Abbot by Abbot v. Am. Cyanamid Co., 844 F.2d 1108 (4th Cir.1988) is similarly distinguishable to the instant matter because there, the Court was faced with a preemption analysis specific to vaccines. Notably, as the Abbot Court pointed out, Congress expressly dealt with vaccines in 1986 and 1987 and did not preempt state law; thus, the legislative intent surrounding vaccines weighed against preemption. Further, the Court's holding ultimately stands for the proposition that preemption is not *automatic*, as the Court stated that "[p]reemption does not follow *immediately* from the comprehensive federal regulation of prescription biological products. Every subject that merits congressional legislation is, by definition, a subject of national concern. That cannot mean, however, that every federal statute [automatically] ousts all related state law." *Id.* at 1112

Accordingly, because Plaintiffs' design defect and other non-failure to warn claims are entirely based, and ultimately hinge, on the adequacy of Fosamax's warning, these claims are preempted and must fail as a matter of law. Regardless of what state law applies to each Plaintiff's individual design defect and other non-failure to warn claims, Merck simply cannot be liable for not having a warning on its product that was rejected by the FDA as of the date of a Plaintiff's injury. Because the Court has already found that pursuant to *Wyeth v. Levine*, clear evidence exists

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(emphasis suppl ied) (i nternal citation omitted). The other cases cited to by Plaintiffs' reach a similar conclusion when dealing with vaccines. *See Hurley v. Lederle Labs. Div. of Am. Cyanamid Co.*, 863 F.2d 1173, 1178 (5th Cir.1988) ("... we believe that any case for preemption is doomed by the National Childhood Vaccine Injury ["NCVI"] Act of 1986."); Graham by *Graham v. Wyeth Labs., Div. of Am. Home Products Corp.*, 906 F.2d 1399, 1405 (10th Cir.1990) (indicating that federal preemption does not automatically apply to bar plaintiff's state tort law claims relating to an improperly manufactured vaccine just because such vaccine met the FDA's minimum standards. (emphasis supplied)).

Similarly *Wimbush v. Wyeth*, 619 F.3d 632 (6th Cir.2010) dealt with whether state law claims relating to negligence by a defendant that occurred prior to FDA approval are preempted by the FDA's subsequent approval of the drug. There, the Court specifically stated that it "hold[s] *merely* that FDA approval does not *automatically* preempt state law tort claims for negligence." *Id.* at 646 (emphasis supplied). Further, the Court notes that, of all the cases cited to by Plaintiffs' in support of their argument that design defect claims are not preempted by the FDCA, *Wimbush* is the only case that was decided after *Wyeth v. Levine*, 555 U.S. 555, 129 S.Ct. 1187, 173 L.Ed.2d 51 (2009), and notably, *Wimbush* has the most narrow holding with respect to preemption.

that the FDA would have rejected a stronger warning label, and the crux of Plaintiffs' design defect and non-failure to warn claims is the adequacy of the warning, Defendant is entitled to summary judgment on these claims.

C. Adverse Reaction and Long–Term–Use Failure to Warn Arguments

Plaintiffs argue that their failure to warn claims cannot be preempted because *Glynn* was specific to Merck's failure to update the Precautions section of the Fosamax label, but that Merck has not met its burden to show clear evidence exists that the FDA would have rejected a change to the Adverse Reactions section of the label or a change relating to the long-term use/shifting risk-benefit profile of Fosamax. While Plaintiffs acknowledge that Merck did in fact update the Adverse Reactions section of the Fosamax label in June 2009, Plaintiffs argue that a genuine dispute of fact exists as to whether Merck could have updated the Adverse Reactions section of the label *before* that time.

i. Adverse Reaction and Long–Term Use Analysis

There are several issues surrounding Plaintiffs' arguments. First, as stated above, Merck updated the Adverse Reactions section of its label in June, 2009. The OTSC has instructed Plaintiffs' with injuries occurring prior to September 14, 2010, to show cause why their claims should not be preempted. Upon review of the Plaintiffs' listed in Appendix A of the OTSC, nearly half of them have injuries which occurred between June, 2009 and September 14, 2010. Thus, to state that Plaintiffs'

failure to warn claims are not preempted because they are based on the Adverse Reactions section of the label and not the Precautions section is illogical. Rather, almost half of the Plaintiffs identified in the OTSC were injured when there was *already* an Adverse Reactions warning on the label[9]; therefore, the only plausible failure to warn claims available to such Plaintiffs would have to be based on the Precautions section.

Second, to the extent that Plaintiffs' injuries occurred prior to the June, 2009 Adverse Reactions label change, Plaintiffs assert that there is evidence showing that a fact question exists with regard to whether Merck should have updated this section of the label sooner. As an initial matter, Plaintiffs do not plead this theory of liability in any of their complaints, nor have Plaintiffs set forth evidence indicating that any doctor would not have prescribed Fosamax if the occurrence of low-energy femoral shaft fractures had been mentioned in the Adverse Reactions section prior to 2009. Further, Plaintiffs' argument is one that was already made—also at the last hour—in *Glynn* and, prior to trial, Plaintiffs asserted that the evidence would show that Merck should have acted sooner to report the information it was receiving about fractures to the FDA. *Hearing Tr.*, 71:20–22; 72:8–10, March 8, 2013 ("M R. HONNOLD: The argument is, is the data was clearly there and **the evidence will be** Merck did not act upon it ... it could have and should have been done

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[9] Plaintiffs do not dispute the adequacy of the Adverse Reactions label.

differently based upon the information that Merck had in its possession and sat on and did nothing with.") (emphasis supplied); see also *Plaintiff's Preemption Supplement in Opposition to Defendant's Motion for Summary Judgment Based Upon Federal Preemption, Rule 50(a), and Rule 50(b) Motions* [docket # 218 at 11–5304] ("[T]here is considerable evidence demonstrating that Merck should have at a minimum updated the [A]dverse [R]eactions section of its label as early as 1999.").

This argument is again dependent on the communication of information between *Merck* and the *FDA*, and is of no consequence to the individual Plaintiff. Plaintiffs presented evidence on this issue during the *Glynn* trial and argued that such evidence proves that Merck should have acted sooner; however, this Court was not convinced. The argument being presented by Plaintiffs now is no different than that which was already considered in *Glynn* because the evidence relevant to this claim is what *Merck* submitted to the *FDA* and such communications are the exact same regardless of which Plaintiff is before the Court. Thus, as in *Glynn*, the Court is still not convinced and Plaintiffs cannot recharacterize their failure to warn claims at this stage of the litigation as one involving the Adverse Reactions section of the label in order to overcome the preemption issue. *See In re Fosamax Prods. Liab. Litig. (Boles v. Merck & Co.)*, 2010 WL 1257299, at *5 (S.D.N.Y. Mar.26, 2010) ("[Plaintiff] cannot recharacterize her claim during trial in an effort to overcome the lack of evidence ...").

Third, Plaintiffs' risk-benefit argument surrounding the efficacy of Fosamax was also already considered in *Glynn*. The Court did not accept Plaintiffs' efficacy argument in *Glynn* for the same reason it will not accept this argument here: the omission of efficacy information does not constitute a failure to warn about a drug's risks and therefore, does not raise a genuine issue of material fact as to whether Plaintiffs' failure to warn claims are preempted. *See LaBarre v. Bristol–Myers Squibb Co.*, 2013 WL 6053840, at * 4 (3d Cir. Nov.18, 2013) ("In short, [the drug's] efficacy is irrelevant to [Plaintiff's] failure to warn claim, and the physicians' purported lack of information about it is of no consequence to the adequacy of the warnings.").

In sum, Plaintiffs' contention that the Adverse Reaction section of the label should have been updated prior to 2009, or that efficacy information should have been communicated on the Fosamax label, do not fall outside the scope of *Glynn* and the OTSC nor do they raise genuine issues of material fact with regard to whether clear evidence exists that the FDA would have rejected a label change. Accordingly, Plaintiffs' failure to warn claim(s) are preempted.

D. Warnings and Precautions Failure to Warn Arguments

Plaintiffs argue that their failure to warn claims are not preempted because communications from the FDA reflect that clear evidence does not exist as to whether the FDA would have rejected a warning that was accurately stated and properly supported by Merck. In support of this argument, Plaintiffs

contend that Merck misstated the relevant risk in its PAS submission and the FDA's rejection of Defendant's proposed label is not clear evidence because the agency lacked information to make an informed judgment.

i. Warnings and Precautions Failure to Warn Analysis

Plaintiffs' argument that its claims are not preempted because clear evidence does not exist as to whether the FDA would have rejected a stronger warning to the Precautions section of the label is nothing more than an attempt to gain a second bite at the apple. Plaintiffs fail to raise any facts and/or arguments with regard to the Precautions section of the label that were not already considered and rejected by this Court. Plaintiffs assert that there is new evidence which was not before the Court in *Glynn* that changes the Precautions analysis; however, the "new evidence" provided by Plaintiffs is merely expert opinion on the very same evidence that existed in *Glynn*. Stated differently, while Plaintiffs were able to find an expert to agree with their contention that Merck should have acted differently with respect to updating the Precautions section of its warning, they did not set forth any evidence which suggests that *the FDA* thought the same. The evidence surrounding whether the FDA felt that a label change was necessary remains unchanged, and importantly, provides clear evidence that the FDA *would have* rejected a stronger Precautions warning because the FDA *did* reject a stronger Precautions warning. *See Glynn*, 2013 WL 3270387, at *7 ("the [fact that the] FDA never required Defendant to

submit new language or change the label [ ] demonstrate [s] that the FDA did not think that the label should have been changed at that time.").

Plaintiffs further rely on this new expert opinion to argue that a fact question exists as to whether Merck should have warned about the risk of fractures associated with Fosamax by way of a CBE submission while the FDA decided on class labeling. Again, however, the Court already rejected this argument in *Glynn* and stated that "since the FDA rejected Defendant's PAS, it would not have approved a CBE seeking to add the same language to the label that it just rejected in the PAS, and any changes Defendant made using the CBE supplement would cause the drug to be misbranded." *Id.* at * 8.

Moreover, to the extent that Plaintiffs claim that Merck withheld information from the FDA and clear evidence does not exist as to whether the FDA, if fully informed, would have rejected a stronger label, this does not defeat Defendant's showing that it is entitled to judgment as a matter of law on preemption grounds. As an initial matter, Defendant disputes that it withheld information from the FDA; however, even assuming it did, Plaintiffs have failed to show that providing such information to the FDA would have changed the FDA's conclusion that a Precaution was not warranted. Instead, Plaintiffs' contention appears to be a fraud-on-the FDA theory which was rejected by the Supreme Court in *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 121 S.Ct. 1012, 148 L.Ed.2d 854 (2001), or alternatively, is based largely on speculation and cannot defeat summary judgment. *See Webster v.*

Pacesetter, Inc., 259 F .Supp.2d 27, 37 (D.D.C.2003) ("Nor can plaintiffs create an issue of fact regarding their defective warning claim by speculating that *if* the FDA had known of the delayed perforation and tamponade incidents during the clinical trials and *if* defendant had investigated all the adverse incidents, the FDA would have either recalled the lead or placed it on alert." (emphasis in original)); *In re Trasylol Products Liab. Litig.*, 2010 WL 4259332 (S.D.Fla. Oct.21, 2010) ("[An expert] may not speculate as to what the FDA would have done in hypothetical circumstances.").

Accordingly, Plaintiffs have failed to show that there is a genuine dispute of fact surrounding failure to warn claims based on the Precautions section of the label. Thus, these claims are preempted and Defendant is entitled to judgment as a matter of law.

IV. CONCLUSION

For the reasons outlined above, Defendant is entitled to judgment as a matter of law on all claims made by the Plaintiffs listed in Appendix A of the OTSC with injuries that occurred prior to September 14, 2010, because Plaintiffs have failed to show cause why their claims are not preempted under this Court's ruling in *Glynn*. An appropriate Order accompanies this Opinion.

All Citations

Not Reported in F.Supp.2d, 2014 WL 1266994

APPENDIX D

In re FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION.

Bernadette Glynn and Richard Glynn, Plaintiffs,

v.

Merck Sharp & Dohme Corp, Defendant.

Civil Action Nos. 11–5304, 08–08.

United States District Court,
D. New Jersey.
June 27, 2013.

Donald A. Ecklund, James E. Cecchi, Carella Byrne Cecchi Olstein Brody & Agnello, P.C., Roseland, NJ, Christopher A. Seeger, David R. Buchanan, Seeger Weiss LLP, Newark, NJ, Edward Braniff, Weitz & Luxenberg, New York, NY, for Plaintiffs.

David J. Heubeck, Venable LLP, Baltimore, MD, Karen A. Confoy, Fox Rothschild LLP, PC, Lawrenceville, NJ, for Defendant.

OPINION

PISANO, District Judge.

Plaintiffs Bernadette Glynn and Richard Glynn ("Plaintiffs") brought this lawsuit against Defendant Merck, Sharp, & Dohme Corp. ("Defendant"), the manufacturer of Fosamax, which is a drug approved by the United States Food and Drug Administration ("FDA") for the treatment and prevention of osteoporosis. This matter is part of the multi-district litigation ("MDL") concerning Fosamax and involves allegations that Fosamax causes atypical femur fractures ("AFFs'[1]"), it caused Plaintiff Mrs. Glynn's femur fracture, and Defendant failed to warn physicians about Fosamax and AFFs. Presently before the Court is Defendant's Motion for Summary Judgment based upon Federal Preemption [docket # 25], Motion for Judgment as a Matter of Law pursuant to Rule 50(a) [docket # 198], Renewed Motion for Judgment as a Matter of Law pursuant to Rule 50(a) [docket # 209], and Renewed Motion for Judgment as a Matter of Law pursuant to Rule 50(b) [docket # 216]. The issue in these Motions and before the Court is whether there is clear evidence that the FDA would not have approved a stronger warning to the Fosamax label, thereby warranting preemption of Plaintiffs' failure to warn claim. *See Wyeth v. Levine*, 555 U.S. 555, 129 S.Ct. 1187, 173 L.Ed.2d 51 (2009). This Court heard oral argument on the federal preemption issue on March 8, 2013 and reserved decision until a trial record had been established.

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[1] The abbreviation of atypical femur fracture (singular) is "AFF."

See Fed.R.Civ.P. 78. A jury trial took place from April 8, 2013 to April 29, 2013. On April 29, 2013, the jury returned a verdict for Defendant, finding that Plaintiff did not prove by a preponderance of the evidence that she experienced an AFF in April 2009. Because the record contains clear evidence that the FDA would not have approved a stronger warning to the Precautions section of the Fosamax label, this Court grants the Motions on federal preemption.

I. BACKGROUND[2]

A. Fosamax Approval & Mrs. Glynn's Fosamax Use

In September 1995, the FDA approved Fosamax for the treatment of osteoporosis in postmenopausal women, and in April 1997, the FDA approved Fosamax for the prevention of osteoporosis in postmenopausal women. Since this time, Fosamax has remained FDA approved for the treatment and prevention of postmenopausal osteoporosis.

In 2002, Dr. Murat Acemoglu first prescribed Fosamax to Mrs. Glynn after diagnosing her with "osteopenia—osteoporosis" [docket # 27, Confoy Dec., Ex. 27 & 28]. Mrs. Glynn took Fosamax until April 17, 2009, when she fractured her right femur. Final Pretrial Order ¶ 3.

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[2] This Background section contains facts that pertain to the federal preemption issue. For a more complete discussion of the facts of this case, see this Court's Opinion dated April 11, 2013, 2013 WL 1558697 [docket # 183].

B. History of Fosamax Label Change

On June 13, 2008, the FDA contacted Defendant and other bisphosphonate [3] manufacturers and requested any investigations they conducted "regarding the occurrence of atypical fractures with bisphosphonate use," any investigational plans, and "all hip and femoral fracture case reports" they received [docket # 26, Declaration of Karen A. Confoy in Support of the Motion for Summary Judgment and Motion for Summary Judgment Based Upon Federal Preemption ("Confoy Dec."), Ex. 5; docket # 27, Confoy Dec., Ex. 4]. The FDA also asked that Defendant and the other bisphosphonate manufacturers make an effort where possible "to clarify the fracture location and the duration of bisphosphonate exposure for all case reports." *Id.* The FDA explained that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates" and is "concerned about this developing safety signal." *Id.*

On July 18, 2008, Defendant responded to the FDA's request and included summary tables of clinical and post-marketing data, clinical Council for International Organizations of Medical Sciences ("CIOMS") reports, and post-marketing CIOMS reports [docket # 27, Confoy Dec., Ex. 6]. The FDA's review of this data as well as the data from other bisphosphonate manufacturers "did not show an increase in . . . [the risk of atypical subtrochanteric femur fractures] in women using these medications" [docket # 26, Confoy Dec., Ex. 7].

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[3] Fosamax belongs to a class of drugs known as bisphosphonates.

On September 15, 2008, Defendant submitted a Prior Approval Supplement ("PAS") to the FDA, proposing "to add language to both the Precaution[s] and Adverse Reactions/Post–Marketing Experience section[s] of the label to describe low-energy" subtrochanteric femoral fractures [docket # 27, Confoy Dec., Ex. 8]. Defendant explained that "[i]t is not possible with the present data to establish whether treatment with" Fosamax "increases the risk of [these] . . . low-energy subtrochanteric and/or proximal shaft fractures," but because there is a temporal association between these fractures and Fosamax, Defendant thought that it was "important to include an appropriate statement about them in the product label." *Id.* Defendant sought to add the following language to the Precautions section of the label:

> Low–Energy Femoral Shaft Fracture
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonatetreated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use,

> previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopaedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.
>
> [*Id.*]

Additionally, Defendant proposed adding "low-energy femoral shaft fracture" to the Adverse Reactions/Post–Marketing Experience section of the label and the following statement to the Patient Package Insert: "Patients have experienced fracture in a specific part of the thigh bone. Call your doctor if you develop new or unusual pain in the hip or thigh." *Id.*

On April 15, 2009, an FDA representative e-mailed Defendant and stated that the proposed label change to the Adverse Reactions/Post–Marketing Experience section of the label would be approved but the label change to the Precautions section would not be approved [docket # 101, Cecchi Dec., Ex. 83; docket # 27, Confoy Dec., Ex. 10]. Two days later, Mrs. Glynn fractured her femur.

On May 22, 2009, one month after Mrs. Glynn's fracture, the FDA formally responded to Defendant's proposed label change, recommending that it add "low energy femoral shaft and subtrochanteric fractures" to the Adverse Reactions/Post–Marketing Experience section of the label; however, the FDA did not approve the label change to the Precautions section [docket # 27, Confoy Dec., Ex. 11]. Moreover,

the FDA warned that Fosamax "may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if [it is] ... marketed with" these label changes "before [FDA] approval. . . ." *Id.*

On July 2, 2009, Defendant submitted to the FDA a Changes Being Effected ("CBE") supplement to add information about femur fractures to the Adverse Reactions/Post–Marketing Experience section of the label because the FDA told Defendant that submitting a CBE supplement was the "quickest route to update the [Product Circular] PC" for Fosamax [docket # 27, Confoy Dec., Ex. 12]. On March 1, 2010, the FDA approved the CBE supplement [docket # 26, Confoy Dec., Ex. 9].

On March 10, 2010, the FDA issued a Drug Safety Communication, in which it stated that "[a]t this point, the data that FDA has reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures" [docket # 26, Confoy Dec., Ex. 5]. The FDA did state, however, that it was "working closely with outside experts, including members of the ... American Society of Bone and Mineral Research Subtrochanteric Femoral Fracture Task Force, to gather additional information that may provide more insight into this issue." *Id.*

On September 14, 2010, the American Society for Bone and Mineral Research ("ASBMR") published an article entitled *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral*

Research [docket # 26, Confoy Dec., Ex. 13].[4] The report stated that although there is an association between long-term bisphosphonate use and AFFs, the association has "not been proven to be causal." *Id.* at 2269, 2287. The report concluded that although AFFs are rare, "they appear to be more common in patients who have been exposed to long-term BPs [("bisphosphonates")], usually for more than 3 years. . . ." *Id.* at 2287. The report further provided that although "BPs are important drugs for the prevention of common osteoporotic fractures," "atypical femoral fractures are of concern, and more information is urgently needed both to assist in identifying patients at particular risk and to guide decision making about duration of BP therapy.

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[4] In this report, the ASBMR defined AFF by listing its Major Features, which are required to satisfy the definition of AFF, and Minor Features, which may be associated with AFFs but are not required characteristics of them [docket # 26, Confoy Dec., Ex. 13]. The Major Features of an AFF are: (1) that it is "located anywhere along the femur from the distal to the lesser trochanter to just proximal to the supracondylar flare"; (2) "associated with no trauma or minimal trauma, as in a fall from a standing height or less"; (3) transverse or short oblique configuration; (4) noncomminuted; and (5) complete fractures extend through both cortices and may be associated with a medial spike, incomplete fractures involve only the lateral cortex. *Id.* The Minor Features of an AFF are: (1) localized periosteal reaction of the lateral cortex; (2) generalized increase in cortical thickness of the diaphysis; (3) prodromal symptoms such as dull or aching pain in the groin or thigh; (4) bilateral fractures and symptoms; (5) delayed healing; (6) comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hyposphosphotasia); and (7) use of pharmaceutical agents (e.g., bisphosphonates, glucocorticoids, and proton pump inhibitors). *Id.*

Physicians and patients should be made aware of the possibility of atypical femoral fractures and of the potential for bilaterality through a change in labeling of BPs." *Id.*

The FDA responded to the report by issuing a Drug Safety Communication, in which it stated "[a]lthough it is not clear if bisphosphonates are the cause [of AFFs], these unusual femur fractures have been identified in patients taking these drugs" [docket # 26, Confoy Dec., Ex. 14]. Additionally, the FDA informed that the "optimal duration of bisphosphonate treatment for osteoporosis is unknown" but "clinical trial data . . . support[s] effectiveness for the reduction of common bone fractures for three to five years." *Id.* Regarding the ASBMR Task Force's recommendation of a label change, the FDA stated that it "has assembled and is thoroughly reviewing all long term data available on the products, as well as all safety reports, and *is considering* label revisions." *Id.* (emphasis added).

In October 2010, the FDA issued another Drug Safety Communication, informing that it would require all bisphosphonate manufacturers to add information on AFFs to the Precautions section of the drug labels and require a new Limitations of Use statement in the Indications and Usage section of the label because "these atypical fractures may be related to long-term . . . bisphosphonate use" [docket # 26, Confoy Dec., Ex. 15]. It reiterated that "[a]lthough it is not clear if bisphosphonates are the cause, these unusual femur fractures have been predominantly reported in patients taking bisphosphonates." *Id.* On January 11, 2011, Defendant submitted the agreed upon label changes to the FDA [docket # 27,

Confoy Dec., Ex. 18]. Also in January 2011, the FDA issued an update on femur fractures and bisphosphonate use, stating "[a]lthough it is not clear that the drugs are a direct cause of these unusual fractures, they have mainly been reported in patients taking bisphosphonates" [docket # 26, Confoy Dec., Ex. 19].

Currently, the Fosamax label includes the following language: "Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. . . . Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates. Atypical femur fractures most commonly occur with minimal or no trauma to the affected area" [docket # 26, Confoy Dec., Ex. 20].

C. Procedural History

On September 15, 2011, Plaintiffs filed a Complaint in this Court against Defendant, alleging causes of action for: (1) failure to warn; (2) defective design; (3) negligence; (4) negligent misrepresentation; (5) breach of express warranty; (6) breach of implied warranty of fitness for a particular purpose; (7) breach of implied warranty of merchantability; (8) violation of the Consumer Fraud Act, N.J.S.A. 56:8–2 et seq.; (9) violations of the New York General Business Law, N.Y. Gen. Bus. Law §§ 349 et seq. and 350 et seq.; (10) unjust enrichment; (11) punitive damages pursuant to the New Jersey Product Liability Act, N.J.S.A. 2A:58C–1 et seq., and the New Jersey Punitive Damages Act, N.J.S.A. 2A:15–5.10, et seq.; and (12) loss of

consortium on behalf of Plaintiff Richard Glynn [docket # 1]. [5] Defendant moved for summary judgment based on federal preemption on January 15, 2013, arguing that Plaintiffs' claims, all of which ultimately concern a failure to warn, are preempted because the FDA rejected Defendant's proposed label change and this constitutes clear evidence that the FDA would not have approved a stronger warning to the Precautions section of the label [docket # 25]. On March 8, 2013, the Court heard argument on the preemption issue and reserved decision on it [docket # 138]. On April 2, 2013, the Court reserved decision on the federal preemption motion until there was a complete trial record in the case [docket # 156].

Trial began on April 8, 2013 and concluded on April 29, 2013. After the close of the Plaintiff's case, on April 20, 2013, Defendant filed a Motion for Judgment as a Matter of Law pursuant to Federal Rule of Civil Procedure 50(a) [docket # 198]. Defendant argued that although it submitted to the FDA all the information relevant to a label change and tried to change the Precautions section of the label to include low-energy femoral fractures, the

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[5] Subsequently, Plaintiffs decided to pursue only the following claims: (1) failure to warn; (2) breach of the implied warranty of fitness for a particular purpose; (3) violations of the New York General Business Law; and (4) punitive damages. The Court granted summary judgment on the New York General Business Law claims [docket # 183]. In addition, the Court granted a Motion for Judgment as a Matter of Law as to the breach of implied warranty of fitness for a particular purpose claim and punitive damages [docket # 198]. Trial Tr. 1896:2–17; 2586:20–22. Thus, the failure to warn claim is the only claim that remains. Trial Tr. 2586:11–12.

FDA rejected the label change. On April 26, 2013, Defendant renewed its Motion for Judgment as a Matter of Law, again arguing that Plaintiffs' claims are preempted because Defendant proposed a change to the Precautions section of the Fosamax label and the FDA rejected it [docket # 209]. On April 29, 2013, the jury returned a verdict for Defendant, finding that Plaintiffs did not prove by a preponderance of the evidence that Mrs. Glynn experienced an AFF in April 2009. The following day, the Court held an in-person status conference to discuss the preemption issue as well as other MDL issues. The Court explained that it previously deferred decision on the preemption issue for "a complete record" and "the best way to do that was to try the" case. Hearing Tr., 6:10–14, April 30, 2013. Although Plaintiffs had several opportunities to present evidence on preemption, they requested additional time to present more evidence on the issue. The Court gave Plaintiffs twenty-one days to submit "proposed fact findings that are based upon the record in opposition to" the preemption motions. *Id.* at 19:24–20:1. Thereafter, on May 6, 2013, Defendant submitted a Renewed Motion for Judgment as a Matter of Law pursuant to Rule 50(b) [docket # 216]. Plaintiffs submitted an opposition brief and Defendant submitted a reply brief.

II. DISCUSSION

A. Standard

"If a court does not grant a motion for judgment as a matter of law made under Rule 50(a), the court is considered to have submitted the action to the jury

subject to the court's later deciding the legal questions raised by the motion." Fed.R.Civ.P. 50(b). The movant may then file a renewed motion for judgment as a matter of law, and in "ruling on the renewed motion, the court may: (1) allow judgment on the verdict, if the jury returned a verdict; (2) order a new trial; or (3) direct the entry of judgment as a matter of law." *Id.*

B. Plaintiffs' Claims Are Preempted

Defendant argues that Plaintiffs' claims are preempted under federal law because it proposed a label change to the Precautions section of the Fosamax label to include a warning about low-energy femur fractures, and the FDA rejected the label change after Mrs. Glynn's fracture. Defendant asserts that this constitutes clear evidence that the FDA would have rejected any warning about these fractures prior to Mrs. Glynn's femur fracture. Moreover, Defendant contends that Plaintiffs' claims are preempted for three additional reasons: (1) Plaintiffs did not present evidence that the FDA rejected the proposed label change for using the phrase "stress fracture" as opposed to AFF; (2) Plaintiffs did not show that the label change could have been successfully presented through a CBE supplement; and (3) Plaintiffs did not show that Defendant withheld any information from the FDA.

Plaintiffs, however, argue that Defendant has not shown clear evidence that the FDA would have rejected language about AFFs in the Precautions section of the Fosamax label prior to Mrs. Glynn's fracture. Plaintiffs assert that preemption is improper for the following reasons: (1) the FDA

rejected the PAS because Defendant used the phrase "stress fracture" instead of "atypical" fracture, and the FDA would have approved an appropriately worded warning; (2) Defendant could have changed the label through a CBE supplement; (3) Defendant did not provide all of the information it had on femur fractures and Fosamax to the FDA, and had it done so, the FDA would have approved a properly worded warning in 2008; and (4) Defendant failed to warn the FDA as soon as there was reasonable evidence of a causal association between Fosamax and AFFs.

Defendant submitted a reply brief, again arguing that preemption is proper because Defendant proposed a label change in 2008 and the FDA rejected it in 2009, after Mrs. Glynn's fracture. Defendant asserts that the FDA did not reject the label change because Defendant used the phrase "stress fracture" since references to "stress fractures" were included to aid in the early identification of low-energy femur fractures. Moreover, Defendant contends that it did not fail to submit information to the FDA. Lastly, Defendant points out that the evidence Plaintiffs presented in their brief was not introduced at trial and thus, is not properly before this Court on this Motion; even if it was properly before this Court, the evidence does not change the fact that clear evidence exists that the FDA would not have approved a stronger warning to the Fosamax label.

[1-6] The Supremacy Clause provides that the "Constitution, and Laws of the United States . . . shall be the supreme Law of the Land. . . ." U.S. Const. art. VI, cl. 2. It "invalidates state laws that interfere with, or are contrary to, federal law." *Hillsborough County, Florida v. Automated Medical*

Laboratories, Inc., 471 U.S. 707, 712, 105 S.Ct. 2371, 85 L.Ed.2d 714 (1985) (internal quotation omitted). Federal law preempts state law in three ways: (1) express preemption; (2) field preemption, and (3) conflict preemption. *Farina v. Nokia Inc.*, 625 F.3d 97, 115 (3d Cir. 2010), *cert. denied*, —— U.S. ——, 132 S.Ct. 365, 181 L.Ed.2d 231 (2011); *Dobbs v. Wyeth Pharmaceuticals*, 797 F.Supp.2d 1264, 1268 n. 3 (W.D.Okla.2011). Express preemption occurs when Congress states "in express terms" that it is preempting state law. *Hillsborough County, Florida*, 471 U.S. at 713, 105 S.Ct. 2371. Field preemption occurs when Congress intends to preempt state law "in a particular area" or in other words "the scheme of federal regulation is sufficiently comprehensive . . . [so] Congress 'left no room' for supplementary state regulation." *Id.* Conflict preemption is when a "state law is in actual conflict with federal law"; this exists "where it is impossible for a private party to comply with both state and federal requirements . . . or where state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Sprietsma v. Mercury Marine, a Div. of Brunswick Corp.*, 537 U.S. 51, 64, 123 S.Ct. 518, 154 L.Ed.2d 466 (2002) (internal quotation omitted). This case concerns conflict preemption because Defendant argues that it was impossible to comply with the state law duty to warn and the FDA's regulations[6] since Plaintiffs argue that

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[6] Federal regulations "preempt state laws in the same fashion as congressional statutes." *Farina*, 625 F.3d at 115 (citing *Fid. Fed. Sav. & Loan Ass'n. v. de la Cuesta*, 458 U.S. 141, 153, 102 S.Ct. 3014, 73 L.Ed.2d 664 (1982)).

a warning about low-energy femur fractures should have been included in the Fosamax label but the FDA rejected a proposed warning.

[7,8] Conflict preemption, however, "is a demanding defense." *Wyeth*, 555 U.S. at 573, 129 S.Ct. 1187. As a result, generally, FDA approval or compliance with FDA labeling regulations is not a complete defense to a state failure to warn claim. *Id.* at 559, 129 S.Ct. 1187. If, however, there is "clear evidence that the FDA would not have approved a change" to the prescription drug's label, then it is impossible to comply with both federal and state requirements[7] and the state failure to warn claim is preempted. *Id.* at 571, 129 S.Ct. 1187. *Wyeth* does not define "clear evidence," so "application of the clear evidence standard is necessarily fact specific." *Dobbs*, 797 F.Supp.2d at 1270.

[9] Here, preemption is warranted because there is clear evidence that the FDA would not have approved a change to the Precautions section of the Fosamax label prior to Mrs. Glynn's fracture. In September 2008, Defendant submitted a PAS to the FDA, seeking to add language about low-energy femur fractures to the Precautions and Adverse Reactions sections of the label. In May 2009, approximately one month after Mrs. Glynn's fracture, the FDA sent Defendant a letter approving the change to the Adverse Reactions section of the label but denying

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[7] Federal regulations require that a drug's label "be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." 21 C.F.R. § 201.57.

the change to the Precautions section of the label. The FDA's rejection constitutes clear evidence that the FDA would not have approved a label change to the Precautions section of the label prior to Mrs. Glynn's injury. *See Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 873 (7th Cir.2010) (finding clear evidence that the FDA would not have approved a label change because the FDA did not approve "a reference to SJS/TEN on the label of over-the-counter drugs containing ibuprofen, when it had been asked to do so in a submission"); *Dobbs*, 797 F.Supp.2d at 1276–77 (finding clear evidence that the FDA would have rejected an expanded warning for Effexor after the FDA rejected the warning added by Defendant); *see also Wyeth*, 555 U.S. at 571–72, 129 S.Ct. 1187 (holding that *Wyeth* "failed to demonstrate that it was impossible for [it] ... to comply with both federal and state requirements" and reasoning that it "offered no such evidence" and never argued "that it attempted to give" a warning but "was prohibited from doing so by the FDA").

Indeed, the evidence presented at trial establishes that the FDA would not have approved a label change to the Precautions section of the Fosamax label prior to Mrs. Glynn's injury. In fact, Dr. Cheryl Blume ("Dr. Blume"), one of Plaintiffs' experts who was "central" to Plaintiffs' preemption analysis, testified that the FDA "rejected" Defendant's PAS. Hearing Tr., 12:24–13:13, April 2, 2013; Trial Tr., 661:10–14. Moreover, Dr. Lisa Rarick ("Dr. Rarick"), one of Defendant's experts who worked for the FDA for fifteen years, testified that the FDA "rejected a precaution" to the Fosamax label in their May 22, 2009 letter to Defendant. Trial Tr., 2436:22–24;

2501:7–9. Dr. Rarick further testified that although the FDA had the authority to ask Defendant to submit "alternative precautionary language" if it was "still contemplating [that] they might accept a precaution," the FDA did not do so, thereby indicating that it would not accept a label change to the Precautions section of the Fosamax label at that time. *Id.* at 2501:10–2502:1. Furthermore, Dr. Rarick testified that the FDA had the authority to request that Defendant "make a label change to include reports of low-energy spontaneous subtrochanteric or atypical femur fractures," but they never made such a request. *Id.* at 2485:4–8; 2578:2–12. Thus, clear evidence exists that the FDA would not have approved a label change to the Precautions section of the Fosamax label prior to Mrs. Glynn's fracture because Defendant submitted a label change and the FDA rejected it, and the FDA never required Defendant to submit new language or change the label, which demonstrates that the FDA did not think that the label should have been changed at that time.

Plaintiffs did not present any evidence at trial to refute preemption. First, Plaintiffs did not offer any evidence that Defendant's PAS was rejected due to language, specifically the use of "stress fracture" instead of "AFF," or that the FDA would have approved a properly worded label change. Instead, it would have been improper for Defendant to use the term "AFF" in 2008 when they submitted the PAS because, as Dr. Blume testified, the phrase "atypical femur fractures . . . wasn't even contrived until 2010 or 2011." *Id.* at 725:22–24. In addition, Dr. Cornell, the Clinical Director of Orthopaedic Surgery at the Hospital for Special Surgery and one of Plaintiffs'

experts, explained that Fosamax "can lead to . . . subsequent stress fracture formation," and when he wrote about these fractures, he was "talking about atypical femur fractures." *Id.* at 1264:20–1265:8. Moreover, Dr. Rarick testified that in rejecting Defendant's PAS, the FDA did not conclude that the label was "confusing to doctors" or that "stress fractures didn't look as severe and significant as . . . atypical femur fractures"; instead, Dr. Rarick stated that the FDA rejected the PAS because the "data didn't support the precaution language." *Id.* at 2512:10–18. This testimony demonstrates that the FDA did not reject the PAS due to Defendant's use of the phrase "stress fracture." Not only was the phrase AFF not coined in 2008, but some doctors used "stress fracture" as a term to refer to low-energy subtrochanteric fractures.

Second, Plaintiffs did not offer any evidence that Defendant could have submitted a CBE supplement to change the Precautions section of the Fosamax label. A CBE supplement gives a "manufacturer . . . the ability to change the label without FDA approval." *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392 (7th Cir.2010); *Dobbs*, 797 F.Supp.2d at 1271 (citing 21 C.F.R. § 314.70(c)(6)(iii)) (stating it is "an exception to the requirement of advance approval for label changes under certain circumstances"). A CBE supplement "allows a pre-approval label change by the manufacturer where the change is needed to add or strengthen a contraindication, warning, precaution or information about an adverse reaction." *Dobbs*, 797 F.Supp.2d at 1271 (citing 21 C.F.R. § 314.70(c)(6)(iii)(A)). Like a PAS, the "proposed change must be based on 'reasonable evidence of' an

association between a hazard and the drug at issue; however, a causal relationship need not have been definitely established." *Id.* (citing C.F.R. § 201.57(c)(6)(i)). After the label change has been affected, the "FDA has the opportunity to consider whether or not it will accept the change." *Mason*, 596 F.3d at 392. Drs. Blume and Rarick testified that if the FDA rejects a CBE label change, the manufacturer must change the label, otherwise it will be misbranded. Trial Tr. 733:16–734:9; 2502:8–16. Thus, since the FDA rejected Defendant's PAS, it would not have approved a CBE seeking to add the same language to the label that it just rejected in the PAS, and any changes Defendant made using the CBE supplement would cause the drug to be misbranded. In addition, Dr. Rarick testified that the FDA could have requested that Defendant submit the label change using the CBE instead of the PAS method, but the FDA did not do so. *Id.* at 2489:19–22. Moreover, Dr. Rarick opined that the CBE method was not "the appropriate method to submit" a label change regarding low-energy subtrochanteric femur fractures because this "topic . . . was under FDA's review. . . ." *Id.* at 2493:11–22. As a result, the evidence does not show that Defendant could have changed the Precautions section of the Fosamax label using a CBE supplement.

Third, Plaintiffs did not show that Defendant failed to provide all the information it had on femur fractures to the FDA and that Defendant failed to warn the FDA as soon as there was reasonable evidence of a causal association between Fosamax and AFFs. Instead, Dr. Blume and Dr. Santora, Defendant's employee who is responsible for Fosamax,

testified that Defendant supplied the Odvina report, Goh report, Adverse Event Reports, and data it obtained from physicians; Defendant also submitted information when the FDA requested it in 2008. *Id.* at 729:5–730:21; 2175:16–21; 2176:4–10; 2254:15–19; 2261:13–2262:8. Regarding the timing of Defendant's proposed label change, there is no evidence that Defendant failed to submit the label change when it had reasonable evidence of a causal association between Fosamax and femur fractures. Defendant submitted the PAS three months after the FDA requested information from bisphosphonate manufacturers, and as late as March 2010, the FDA did not see a "clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures" [docket # 26, Confoy Dec., Ex. 5].

[10] Not only did Plaintiffs fail to offer any evidence at trial to refute preemption but the exhibits Plaintiffs cited in their opposition brief were not presented at trial [docket # 218]. This is inappropriate on a Motion for Judgment as a Matter of Law where "the court is limited to the trial record and nothing else." *Laymon v. Lobby House, Inc.*, 613 F.Supp.2d 504, 510 (D.Del.2009). Even if the evidence Plaintiffs cited were part of the trial record, this Court is not persuaded that it would change the fact that there is clear evidence that the FDA would not have approved a stronger warning prior to Mrs. Glynn's fracture.

Therefore, preemption is warranted in this case. Defendant submitted a PAS in 2008 seeking to change the Precautions section of the Fosamax label to include information on low-energy subtrochanteric

femur fractures, but the FDA rejected the PAS in May 2009, one month after Mrs. Glynn's fracture. This constitutes clear evidence that the FDA would not have approved a stronger warning prior to Mrs. Glynn's fracture. Although Plaintiffs have had several opportunities to introduce evidence in opposition to preemption, they have not refuted the fact that clear evidence exists. Consequently, based on the record before the Court, Plaintiffs' failure to warn claim is preempted.

III. CONCLUSION

For the reasons outlined above, this Court grants Defendant's Motion for Summary Judgment based upon Federal Preemption [docket # 25], Motion for Judgment as a Matter of Law [docket # 198], second Motion for Judgment as a Matter of Law [docket # 209], and Renewed Motion for Judgment as a Matter of Law [docket # 216] and enters judgment in favor of Defendant. An appropriate Order accompanies this Opinion.

APPENDIX E

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 14-1900

IN RE: FOSAMAX (ALENDRONATE SODIUM)
PRODUCTS LIABILITY LITIGATION

D. N.J. 3:08-cv-00008-FLW *et al.*, MDL No. 2243

SUR PETITION FOR REHEARING

Present: SMITH, Chief Judge, AMBRO, CHAGARES, JORDAN, HARDIMAN, VANASKIE, SHWARTZ, KRAUSE, RESTREPO, FUENTES,* Circuit Judges

The petition for rehearing filed by appellant, in the above-entitled case having been submitted to the judges who participated in the decision of this Court and to all the other available circuit judges of the circuit in regular active service, and no judge who

* Pursuant to Third Circuit I.O.P. 9.5.3., Judge Fuentes' vote is limited to panel rehearing.

concurred in the decision having asked for rehearing, and a majority of the judges of the circuit in regular service not having voted for rehearing, the petition for rehearing by the panel and the Court en banc, is denied.

BY THE COURT,

s/ Julio M. Fuentes
Circuit Judge

Dated: April 24, 2017
CJG/cc: All Counsel of Record

APPENDIX F

21 U.S.C. § 355

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title. . . .

. . .

. . .

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; . . . or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the

labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence. The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for marketing approval of a drug.

. . .

(k) Records and reports; required information; regulations and orders; access to records

(1) In the case of any drug for which an approval of an application filed under subsection (b) or (j) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to

determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section. . . .

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

. . .

(o) Postmarket studies and clinical trials; labeling

(1) In general

A responsible person may not introduce or deliver for introduction into interstate commerce the new drug involved if the person is in violation of a requirement established under paragraph (3) or (4) with respect to the drug.

. . .

(4) Safety labeling changes requested by Secretary

(A) New safety information

If the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug, the Secretary shall promptly notify the responsible person or, if the same drug approved under subsection (b) is not currently marketed, the holder of an approved application under subsection (j).

(B) Response to notification

Following notification pursuant to subparagraph (A), the responsible person or the holder of the approved application under subsection (j) shall within 30 days--

(i) submit a supplement proposing changes to the approved labeling to reflect the new safety information, including changes to boxed warnings, contraindications, warnings, precautions, or adverse reactions; or

(ii) notify the Secretary that the responsible person or the holder of the approved application under subsection (j) does not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted.

(C) Review

Upon receipt of such supplement, the Secretary shall promptly review and act upon such supplement. If the Secretary disagrees with the proposed changes in the supplement or with the statement setting forth the reasons why no labeling change is necessary, the Secretary shall initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes.

(D) Discussions

Such discussions shall not extend for more than 30 days after the response to the notification under subparagraph (B), unless

the Secretary determines an extension of such discussion period is warranted.

(E) Order

Within 15 days of the conclusion of the discussions under subparagraph (D), the Secretary may issue an order directing the responsible person or the holder of the approved application under subsection (j) to make such a labeling change as the Secretary deems appropriate to address the new safety information. Within 15 days of such an order, the responsible person or the holder of the approved application under subsection (j) shall submit a supplement containing the labeling change.

(F) Dispute resolution

Within 5 days of receiving an order under subparagraph (E), the responsible person or the holder of the approved application under subsection (j) may appeal using dispute resolution procedures established by the Secretary in regulation and guidance.

. . .

. . .

. . .

21 CFR § 201.57

The requirements in this section apply only to prescription drug products described in § 201.56(b)(1) and must be implemented according to the schedule specified in § 201.56(c), except for the requirement in paragraph (c)(18) of this section to reprint any FDA–approved patient labeling at the end of prescription

drug labeling or accompany the prescription drug labeling, which must be implemented no later than June 30, 2007.

(a) Highlights of prescribing information. The following information must appear in all prescription drug labeling:

. . .

(6) Indications and usage. A concise statement of each of the product's indications, as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. If the product is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class in the following manner: "(Drug) is a (name of class) indicated for (indication(s))."

. . .

(9) Contraindications. A concise statement of each of the product's contraindications, as required under paragraph (c)(5) of this section, with any appropriate subheadings.

(10) Warnings and precautions. A concise summary of the most clinically significant information required under paragraph (c)(6) of this section, with any appropriate subheadings, including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm.

(11) Adverse reactions.

(i) A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., incidence rate). Adverse reactions important for other reasons (e.g., because they are serious or frequently lead to discontinuation or dosage adjustment) must not be repeated under this heading in Highlights if they are included elsewhere in Highlights (e.g., Warnings and Precautions, Contraindications).

. . .

. . .

(b) Full prescribing information: Contents. Contents must contain a list of each heading and subheading required in the full prescribing information under § 201.56(d)(1), if not omitted under § 201.56(d)(4), preceded by the identifying number required under § 201.56(d)(1). Contents must also contain any additional subheading(s) included in the full prescribing information preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(c) Full prescribing information. The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings, subheadings, and identifying numbers required under § 201.56(d)(1), unless omitted under § 201.56(d)(4). If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(1) Boxed warning. Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.

(2) Indications and usage. This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

(i) This section must include the following information when the conditions listed are applicable:

. . .

(F) If there are specific conditions that should be met before the drug is used on a long term basis (e.g., demonstration of responsiveness to the drug in a short term trial in a given patient), a statement of

the conditions; or, if the indications for long term use are different from those for short term use, a statement of the specific indications for each use.

. . .

(3) Dosage and administration.

(i) This section must state the recommended dose and, as appropriate:

. . .

(F) The usual duration of treatment when treatment duration should be limited,

. . .

. . .

. . .

(6) Warnings and precautions.

(i) General. This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of

the drug, must be expressed as provided under paragraph (c)(7) of this section. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

(ii) Other special care precautions. This section must contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (e.g., precautions not required under any other specific section or subsection).

. . .

(7) Adverse reactions. This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug,

only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

(i) Listing of adverse reactions. This section must list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. The list or lists must be preceded by the information necessary to interpret the adverse reactions (e.g., for clinical trials, total number exposed, extent and nature of exposure).

(ii) Categorization of adverse reactions. Within a listing, adverse reactions must be categorized by body system, by severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency information cannot be reliably determined, adverse reactions must be listed in decreasing order of severity.

(A) Clinical trials experience. This section must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse

reactions that occurred below the specified rate are included, they must be included in a separate listing. If comparative rates of occurrence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined. For adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.

(B) Postmarketing experience. This section of the labeling must list the adverse reactions, as defined in paragraph (c)(7) of this section, that are identified from domestic and foreign spontaneous reports. This listing must be separate from the listing of adverse reactions identified in clinical trials.

. . .

(9) Use in specific populations. This section must contain the following subsections:

. . .

(v) 8.5 Geriatric use.

. . .

. . .

(d) Format requirements. All labeling information required under paragraphs (a), (b), and (c) of this section must be printed in accordance with the following specifications:

(1) All headings and subheadings required by paragraphs (a) and (c) of this section must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Reverse type is not permitted as a form of highlighting.

(2) A horizontal line must separate the information required by paragraphs (a), (b), and (c) of this section.

(3) The headings listed in paragraphs (a)(5) through (a)(13) of this section must be presented in the center of a horizontal line.

(4) If there are multiple subheadings listed under paragraphs (a)(4) through (a)(13) of this section, each subheading must be preceded by a bullet point.

(5) The labeling information required by paragraphs (a)(1) through (a)(4), (a)(11)(ii) through (a)(11)(iv), and (a)(14) of this section must be in bold print.

(6) The letter height or type size for all labeling information, headings, and subheadings set forth in paragraphs (a), (b), and (c) of this section must be a minimum of 8 points, except for labeling information that is on or within the package from which the drug is to be dispensed, which must be a minimum of 6 points.

(7) The identifying numbers required by § 201.56(d) and paragraphs (c)(1) through (c)(18) of this section must be presented in bold print and must precede the heading or subheading by at least two square em's (i.e., two squares of the size of the letter "m" in 8 point type).

(8) The information required by paragraph (a) of this section, not including the information required under paragraph (a)(4) of this section, must be limited in length to an amount that, if printed in 2 columns on a standard sized piece of typing paper (8 1/2 by 11 inches), single spaced, in 8 point type with 1/2–inch margins on all sides and between columns, would fit on one-half of the page.

(9) Sections or subsections of labeling that are identified as containing recent major changes under paragraph (a)(5) of this section must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the new or modified text.

(10) For the information required by paragraph (b) of this section, each section heading must be in bold print. Each subheading within a section must be indented and not bolded.

21 CFR § 314.70

(a) Changes to an approved NDA.

(1)(i) Except as provided in paragraph (a)(1)(ii) of this section, the applicant must notify FDA about each change in each condition established in an approved NDA beyond the variations already provided for in the NDA. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about the change in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the NDA under paragraph (d) of this section.

(ii) The submission and grant of a written request for an exception or alternative under § 201.26 of this chapter satisfies the applicable requirements in paragraphs (a) through (c) of this section. However, any grant of a request for an exception or alternative under § 201.26 of this chapter must be reported as part of the annual report to the NDA under paragraph (d) of this section.

(2) The NDA holder must assess the effects of the change before distributing a drug product made with a manufacturing change.

(3) Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require

approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) and (c) of this section.

(5) Except for a supplement providing for a change in the labeling, the applicant must include in each supplement and amendment to a supplement providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy has been provided in accordance with § 314.440(a)(4).

(6) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the submission.

(b) Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

(2) These changes include, but are not limited to:

. . .

(v) The following labeling changes:

(A) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

(B) If applicable, any change to a Medication Guide required under part 208 of this chapter, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter; and

(C) Any change to the information required by § 201.57(a) of this chapter, with the following exceptions that may be reported in an annual report under paragraph (d)(2)(x) of this section:

(1) Removal of a listed section(s) specified in § 201.57(a)(5) of this chapter; and

(2) Changes to the most recent revision date of the labeling as specified in § 201.57(a)(15) of this chapter.

. . .

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using a change under paragraph (b) of this section. Except for submissions under paragraph (e) of this section, the following information must be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The drug product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to assess the effects of the change;

(v) The data derived from such studies;

. . .

. . .

(c) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

. . .

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement—Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this

section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved NDA may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

. . .

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental NDA, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

. . .

21 C.F.R. § 314.80

(a) Definitions. The following definitions of terms apply to this section:

Adverse drug experience. Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including

the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

. . .

(b) Review of adverse drug experiences. Each applicant having an approved application under § 314.50 or, in the case of a 505(b)(2) application, an effective approved application, must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Applicants are not required to resubmit to FDA adverse drug experience reports forwarded to the applicant by FDA; however, applicants must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section must also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

(c) Reporting requirements. The applicant must submit to FDA adverse drug experience information as described in this section. . . .

. . .

(k) Withdrawal of approval. If an applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

. . .

21 C.F.R. § 314.81

(a) Applicability. Each applicant shall make the reports for each of its approved applications and abbreviated applications required under this section and section 505(k) of the act.

(b) Reporting requirements. The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

. . .

(2) Annual report. The applicant shall submit each year within 60 days of the anniversary date of U.S. approval of the application, two copies of the report to the FDA division responsible for reviewing the application. Each annual report is required to be accompanied by a completed transmittal Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use), and must include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval that ends on the U.S. anniversary date. The report is required to contain in the order listed:

(i) Summary. A brief summary of significant new information from the previous year that

might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study. The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

. . .

(iii) Labeling.

(a) Currently used professional labeling, patient brochures or package inserts (if any), and a representative sample of the package labels.

(b) The content of labeling required under § 201.100(d)(3) of this chapter (i.e., the package insert or professional labeling), including all text, tables, and figures, must be submitted in electronic format. Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic

submission (e.g., method of transmission, media, file formats, preparation and organization of files). Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

(c) A summary of any changes in labeling that have been made since the last report listed by date in the order in which they were implemented, or if no changes, a statement of that fact.

. . .

(v) Nonclinical laboratory studies. Copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product. The applicant shall submit a copy of a published report if requested by FDA.

(vi) Clinical data.

(a) Published clinical trials of the drug (or abstracts of them), including clinical trials on safety and effectiveness; clinical trials on new uses; biopharmaceutic, pharmacokinetic, and clinical pharmacology studies; and reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored

series of patients) conducted by or otherwise obtained by the applicant. Review articles, papers describing the use of the drug product in medical practice, papers and abstracts in which the drug is used as a research tool, promotional articles, press clippings, and papers that do not contain tabulations or summaries of original data should not be reported.

(b) Summaries of completed unpublished clinical trials, or prepublication manuscripts if available, conducted by, or otherwise obtained by, the applicant. Supporting information should not be reported. (A study is considered completed 1 year after it is concluded.)

(c) Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

. . .

. . .

(d) Withdrawal of approval. If an applicant fails to make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

APPENDIX G

RESPONDENTS IN THIS PROCEEDING

Plaintiff	Appeal No.
Albrecht, Doris	14-1900
Molnar, Phyllis	14-2109
Molnar, William	14-2109
Gozdziak, Margaret	14-2110
Duke, Dolores	14-2111
Duke, Thomas	14-2111
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Schultz, Russ	14-2112
Hines, Cynthia H.	14-2113
Hines, Robert N.	14-2113
Goodwin, Joan H.	14-2114
Moline, Barbara R.	14-2115
Moline, Ronald	14-2115
Wheeler, Kathryn K.	14-2117
Denker, Elayne	14-2118
Denker, Stephen	14-2118
Heaton, Nancy	14-2119
Bonne, Virginia	14-2120
Lefebvre, Alice	14-2121
Hogan, Marie	14-2122
Karch, Lillie	14-2123
Walraed, Susan	14-2124

Sullivan, J. Thomas	14-2124
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Kolb, Ralph	14-2126
Dematto, Mary E.	14-2127
Germino, Virginia Lee	14-2128
Chaires, Jeanette S.	14-2129
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Granato, Samuel W.	14-2136
Graves, Barbara	14-2137
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Krieg, Larry E.	14-2147
Cortez, Lorice	14-2148
Hardy, Shirley	14-2149

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Clougherty, Mary Patricia	14-2153
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Onaka, Eleanor	14-2156
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Panouis, Androniki	14-2167
Blackford, June	14-2168
Krakovitz, Pearl	14-2169
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Pisarz, Walter	14-2170
Strominger, Betty	14-2171
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Howe, Elaine F.	14-2177
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Nelson. Gretchen Flint	14-2187
Haviland. Barbara	14-2188
Matney, Rosemary	14-2189
McGill, Barbara	14-2190
Schwalbe, Linda	14-2191
Schwalbe, Robert	14-2191
Nation, Karleen	14-2192
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Burke, Louise Findley	14-2194
Carter-Corcomb. Patty	14-2195
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McKee, Richard	14-2197
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Degen. Patricia	14-2201
Mahan, Caroline	14-2202
Mistretta, Wilma	14-2203

Sorrentino, Theresa	14-2204
Tucker, Assunta	14-2205
Green, Mariella	14-2206
Green, Dewey	14-2206
Greenway, Ann P.	14-2207
Greenway, Ralph N.	14-2207
Ivey, Jane	14-2208
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Driver, William	14-2209
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Skinner, Leone	14-2220
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Thomasson. Jack	14-2241
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Baldridge, Charles A.	14-2244
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Singh, Priscilla	14-2271
Worthington, Renee	14-2272
Worthington, Norman	14-2272
Palmer, Richard	14-2273
James, Claudia	14-2274
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Still, David	14-2290
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Curry, Winford A.	14-2299

Thomas-Walsh, Theresa	14-2300
Walsh, Patrick	14-2300
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Swanson, Wayne	14-2301
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Underhill, Thomas	14-2304
Nord, Elayne Barbara	14-2305
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Andrejasich, Frank	14-2337
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Burleson, Jacqueline R.	14-2354
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Yost, Richard D.	14-2356
Yost, Marilyn P.	14-2356
Richard-Amato, Patricia	14-2357
Wang, Su-Mei	14-2358
Wang, Chan-Hsiung	14-2358
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Zimmerman, Blaine H.	14-2359
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Flower, James	14-2360
Cross, Katherine	14-2361
Mejia, Teresita	14-2362
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Lowell, Dan	14-2371
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Collier, Verne	14-2372
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Sheehan, Yvonne T.	14-2377
Merrell, Preston	14-2378
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Fracaro, Fern	14-2380
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Hubbard, Linda	14-2385
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Halligan, Carla	14-2387
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Gilmer, Marjorie A.	14-2493
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Osburn, Gaile	14-2503
Osburn, William	14-2503
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Latta, Theresa [switched with plaintiff for 14-2405 in 3rd Cir. Appx.]	14-2505
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In The
Supreme Court of the United States

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

DORIS ALBRECHT, ET AL.,
Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Third Circuit

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QUESTION PRESENTED

The label for petitioner's drug Fosamax has included a warning about atypical femoral fractures since 2011, reflecting petitioner's and the Food and Drug Administration's acknowledgment that reasonable evidence exists that Fosamax causes those fractures. Respondents are more than 500 patients who took Fosamax and suffered atypical femoral fractures before the 2011 label change. Respondents assert, among other things, that petitioner should have updated the Fosamax label to add warnings about atypical femoral fractures earlier than it did.

Petitioner concedes that respondents' failure-to-warn claims are not preempted, because it could have added an earlier warning to the Adverse Reactions section of the Fosamax label. Petitioner seeks only to narrow the failure-to-warn claims to exclude consideration of the Warnings and Precautions section. Petitioner contends that the FDA's rejection of a proposed warning about "stress fractures" (which are widely understood to be minor, incomplete fractures, in contrast to the severe atypical femoral fractures suffered by respondents) is clear evidence that the FDA also would have rejected a warning about atypical femoral fractures. The Third Circuit held that factual disputes existed regarding how the FDA would have reacted to a properly worded warning about atypical femoral fractures, and reversed summary judgment on petitioner's preemption defense.

The question presented is:

Whether the Third Circuit accurately assessed the record evidence in determining that petitioner had failed to show that the FDA would have rejected a properly worded warning about atypical femoral fractures.

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Petitioner concedes that respondents' failure-to-warn claims are not preempted insofar as those claims are based on petitioner's failure to update the Adverse Reactions section of the Fosamax label to include atypical femoral fractures. Pet. 13 n.1. Petitioner also does not challenge the Third Circuit's ruling that none of respondents' non-failure-to-warn claims (such as design defect, breach of warranty, and negligence) are preempted. App. 74a. Thus, even if petitioner prevails, it will not win dismissal of any claim of any respondent. This case therefore does not present a broad question regarding the scope of conflict preemption. It presents only the narrow question whether, upon remand to the district court, respondents will be permitted to argue that petitioner should have warned of atypical femoral fractures on one section of the Fosamax label (Adverse Reactions) or two (Adverse Reactions, and Warnings and Precautions).

Even for the Warnings and Precautions section, this is not the typical preemption case where a defendant argues that the scientific evidence that the drug causes the side effect is insufficient to support a warning. Here, petitioner and the Food and Drug Administration ("FDA") have determined that reasonable evidence exists that Fosamax causes atypical femoral fractures, and petitioner has properly included a warning about those fractures on the Fosamax label for more than six years. The only question is whether, as petitioner contends, the FDA would have prevented petitioner from adding a proper warning of atypical femoral fractures at any earlier date than when the FDA mandated that warning.

That question is hypothetical, because petitioner never proposed such a warning. Instead, petitioner proposed a warning only about a different risk —

minor stress fractures. Because petitioner never proposed a warning about "the risk at issue" (Pet. i), and the FDA never rejected such a warning, the question as to which petitioner seeks review is not in fact presented in this case.

The FDA's response to petitioner's proposed stress-fracture warning confirms that conclusion. In the FDA's "Complete Response" letter, in which it was required by regulation to list *all* deficiencies with petitioner's proposal, *see* 21 C.F.R. § 314.110(a)(1), the FDA identified only the inaccurate description of the risk as "stress fractures." C.A.App. 1500-01. Petitioner hypothesizes that the FDA violated its own regulations by submitting a false Complete Response, listing as its only justification what petitioner calls (at 24) a mere "language quibble." According to petitioner, the decision was actually motivated by a concern — contained nowhere in the Complete Response — that the scientific evidence was insufficient to justify *any* warning. When pressed by the Third Circuit for evidence to support this theory, petitioner's counsel pointed to a piece of double hearsay: a memorandum written by petitioner's employee of a telephone conversation that she purportedly had with an FDA official. App. 49a n.125; C.A.App. 1970.

Faced with what can be described most charitably to petitioner as conflicting evidence, the Third Circuit held that factual disputes remained regarding petitioner's preemption defense. In so ruling, the Third Circuit faithfully applied this Court's holding in *Wyeth v. Levine*, 555 U.S. 555 (2009), that failure-to-warn claims against brand-name drug manufacturers are not preempted "absent clear evidence that the FDA would not have approved" a label change. *Id.* at 571. That conclusion followed from

this Court's recognition that the "central premise of federal drug regulation" is "that the manufacturer bears responsibility for the content of its label at all times," *id.* at 570-71, and that the "Changes Being Effected" ("CBE") regulation "provides a mechanism for adding safety information to the label prior to FDA approval," *id.* at 571. Petitioner acknowledges that the Third Circuit applied the "clear evidence" standard, and it identifies no conflict among the lower courts regarding the legal standard for preemption in this context. There is accordingly no need for this Court to review the Third Circuit's decision, which correctly applied this Court's precedent and did not create any circuit conflict.

Moreover, this case would present a poor vehicle for considering the scope of conflict preemption in any event. Petitioner seeks review of just one aspect of the Third Circuit's decision reversing summary judgment. Even if this Court were to grant review in this interlocutory posture and adopt petitioner's position, all of respondents' claims, including claims for failure to warn in the Adverse Reactions section, would remain to be litigated in the district court. In addition, the record on preemption is underdeveloped in these cases because the district court followed the extraordinary procedural path of granting all of the more than 500 respondents just 45 days to show cause why their claims were not preempted. The Third Circuit did not need to consider respondents' objections to this procedure because it held that petitioner had failed to prove preemption, but, if this Court were to grant certiorari, respondents would raise their procedural arguments as an independent basis for affirmance, which may prevent this Court from reaching the question presented. The Court should deny the petition.

STATEMENT

A. Statutory And Regulatory Background

It is and always has been a "central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Wyeth v. Levine*, 555 U.S. 555, 570-71 (2009). An application for FDA approval to market a drug must include proposed labeling that is neither false nor misleading. *See* 21 U.S.C. § 355(b)(1)(F), (d)(7). FDA approval of a drug encompasses approval of the label. *See* 21 C.F.R. § 314.105(b). After approval, a manufacturer may unilaterally, without prior FDA approval, "add or strengthen a contraindication, warning, precaution, or adverse reaction" on the drug label "to reflect newly acquired information," by submitting a supplement under the CBE regulation. *Id.* § 314.70(c)(6)(iii)(A). A manufacturer can also apply for FDA approval to add a warning through a "Prior Approval Supplement" ("PAS"). *Id.* § 314.70(b)(3). Label changes under a CBE supplement are exempted from the PAS prior approval requirement. *Id.* § 314.70(b)(2)(v)(A).

Two sections of the drug label are relevant here: Adverse Reactions, and Warnings and Precautions. The Adverse Reactions section includes a listing of all "undesirable effect[s], reasonably associated with use of a drug." *Id.* § 201.57(c)(7). A manufacturer must include an adverse reaction if "there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event." *Id.* The Warnings and Precautions section contains descriptions of "clinically significant adverse reactions," which must be included "as soon as there

is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." *Id.* § 201.57(c)(6)(i). Those standards also apply to warnings added through a CBE supplement. *Id.* § 314.70(c)(6)(iii)(A).

In 2007, Congress enacted a provision allowing the FDA to require label changes. 21 U.S.C. § 355(*o*)(4). Congress contemporaneously adopted a "[r]ule of construction" that the new provision "shall not be construed to affect the responsibility of the [drug manufacturer] . . . to maintain its label in accordance with existing requirements, including [the CBE regulation]." *Id.* § 355(*o*)(4)(I).

B. Factual History

1. Atypical femoral fractures are severe injuries in which the thigh bone, or femur, breaks in two, despite the absence of any trauma. C.A.App. 1226 (x-rays). In October 2010, the FDA ordered petitioner and all manufacturers of similar drugs (called bisphosphonates) to inform the public in the Warnings and Precautions section of their drug labels of "the risk of atypical fractures of the thigh." C.A.App. 1118. That decision required the FDA to determine that "reasonable evidence of a causal association" existed. 21 C.F.R. § 201.57(c)(6)(i). Petitioner did not challenge this determination and, in January 2011, voluntarily added a warning that "[a]typical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients." C.A.App. 1070. That warning still appears on the Fosamax label today. The preemption question in this case is whether the FDA would have blocked petitioner from adding such a warning at an earlier date.

2. The FDA approved Fosamax in the 1990s to treat and prevent osteoporosis, and the drug is used

most commonly by post-menopausal women. App. 5a. Human bones constantly undergo a remodeling process in which bone breaks down (resorption) and is rebuilt (formation); in post-menopausal women, the rate of resorption often exceeds that of formation, leading to bone loss. *Id.* Fosamax slows resorption in order to reduce bone loss, but it also inhibits bone formation. App. 6a; C.A.App. 865, 1099. Bones frequently develop tiny fractures called "microcracks" that heal naturally through formation, but Fosamax prevents this healing, causing microcracks to accumulate. App. 6a; C.A.App. 865-66. For many patients, years of Fosamax usage can cause such a large accumulation of microcracks that the femur breaks completely, even without trauma, in an atypical femoral fracture. App. 6a; C.A.App. 884.

Petitioner has known since at least 1992 that Fosamax could weaken bone by inhibiting bone remodeling. App. 12a. As early as 1999, petitioner received adverse event reports indicating that long-term Fosamax users were suffering atypical femoral fractures. C.A.App. 874-75. "Between 1995 and 2010, scores of case studies, reports, and articles were published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures." App. 13a. Because of the surge in these previously rare fractures among Fosamax patients, orthopedic surgeons began referring to them colloquially as "Fosamax Fracture[s]." C.A.App. 875-76, 1261.

3. Fosamax's label contained no mention of femur fractures from its approval in 1995 through 2008. App. 12a-14a. In June 2008, the FDA informed petitioner that it was "aware of reports" of bisphosphonate users suffering atypical femoral fractures and was "concerned about this developing safety signal."

App. 14a. In September 2008, petitioner submitted a PAS to the FDA to add mentions of fractures to the Adverse Reactions and Warnings and Precautions sections of the Fosamax label. The proposed Warnings and Precautions language six times referred to the fractures at issue as "stress fractures" and stated that "risk factors" for such stress fractures included "extreme or increased exercise." *See* Pet. 8. As the FDA later explained, characterizing the risk as "stress fractures" would "contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use" because, "for most practitioners, the term 'stress fracture' represents a minor fracture." App. 22a-23a (quoting C.A.App. 1540). Petitioner has acknowledged that, for most physicians, stress fractures "are associated with repetitive stress injury related to exercise (e.g., running) in younger adults, and that this type of stress fracture generally heals well with rest." C.A.App. 1573.

On May 22, 2009, the FDA submitted a "Complete Response" by Dr. Scott Monroe, granting in part and denying in part petitioner's application. App. 18a; C.A.App. 1500-01. The FDA approved the addition of "low energy femoral shaft and subtrochanteric fractures" to the Adverse Reactions section, C.A.App. 1501, reflecting the conclusion that "there is some basis to believe" that Fosamax causes these fractures, 21 C.F.R. § 201.57(c)(7), but the FDA did not approve the proposed Warnings and Precautions language. By regulation, a complete response letter must "describe all of the specific deficiencies that the agency has identified in an application." *Id.* § 314.110(a)(1). The *only* deficiency described by the FDA was that "'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been

reported in the literature" and the "risk factors for stress fractures" were unsupported. App. 18a-19a. Contrary to petitioner's repeated assertions (at 1, 3, 13), the FDA's Complete Response did not mention any doubt about the scientific evidence that Fosamax causes atypical femoral fractures. *See* C.A.App. 1500-01.

The FDA invited petitioner to "resubmit" its application, C.A.App. 1501, and around the same time informed petitioner it would like to "work with" petitioner "on language for a [Warnings and Precautions] atypical fracture language, if it is warranted," C.A.App. 1498. Petitioner rebuffed the FDA's repeated entreaties for further engagement, and "fail[ed] to re-submit a revised CBE or PAS." App. 67a. Thus, the record contradicts petitioner's assertion that the FDA did not "initiate discussions to reach agreement" on alternate warning language and was unwilling to "work with Merck on a warning that would properly warn the public of the risk." Pet. 13, 24.

Petitioner argued below that the FDA denied the PAS on the basis of a concern not expressed in the Complete Response: "that there was no reasonable evidence of a causal link." App. 60a-61a. Petitioner theorized that the only deficiency actually identified in the Complete Response — the misleading characterization of the risk as "stress fractures" — was a mere "language quibble" that had nothing to do with the FDA's decision. App. 61a. Pressed at oral argument for evidence to support this theory, petitioner "stated that the single best piece of evidence" was a piece of double hearsay: "a set of notes, prepared by [petitioner's] employee, recounting a telephone conversation with Dr. Monroe of the FDA — the same official who wrote the [Complete Response]." App. 49a n.125. In that memorandum, the employee,

Charlotte Merritt, wrote that "[t]he conflicting nature of the literature does not provide a clear path forward, and more time will be need [sic] for FDA to formulate a formal opinion on the issue of a precaution around these data." C.A.App. 1971.

4. In March 2010, the FDA stated that it was "working closely with outside experts . . . to gather additional information" about the relationship between bisphosphonates and atypical femoral fractures. C.A.App. 1508. In October 2010, the FDA announced that it would require all bisphosphonate manufacturers to warn of atypical femoral fractures in the Warnings and Precautions section, because "these atypical fractures may be related to long-term . . . bisphosphonate use." App. 20a (alteration in original). The FDA specifically ordered petitioner to add a warning. App. 21a-22a. Petitioner did not dispute the FDA's conclusion that the scientific evidence justified an atypical femoral fracture warning, but petitioner proposed language describing the fractures five times as "stress fractures." App. 22a. The FDA circulated a redline striking out every instance of "stress fractures," explaining that, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use." App. 22a-23a; C.A.App. 1540, 1556-57.[1] Since January 2011, the Warnings and Precautions section of the Fosamax label has included an atypical femoral fracture warning. App. 23a; C.A.App. 1070 (Jan. 2011 label).

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[1] Petitioner omits the fact that it proposed "stress fracture" language a second time, and the FDA rejected its proposed language as misleading. Pet. 11.

C. Procedural History

Respondents are more than 500 individuals who allegedly suffered an atypical femoral fracture caused by Fosamax usage. App. 4a. Respondents filed separate complaints, which were consolidated for pretrial administration in a multi-district litigation ("MDL"). *Id.* Although each complaint is different, respondents assert failure-to-warn claims, as well as several non-warning claims, including design defect, negligence, and breach of warranty. App. 55a-56a. Apart from a small set of designated "Early Discovery Cases," discovery in individual cases has not yet begun. C.A.App. 734.

In 2013, the district court held the first bellwether trial in the *Glynn* case. App. 24a. The jury found that Ms. Glynn failed to prove that she suffered an atypical femoral fracture. App. 25a. Even though the jury had already rejected Ms. Glynn's claims on the merits, the district court issued a post-trial opinion that her claims were preempted. *Id.* Shortly after that opinion, in August 2013, the court issued an order requiring all respondents to show cause why their claims were not preempted. App. 26a. The court gave respondents 45 days to obtain evidence and submit briefs opposing preemption. C.A.App. 769.

The district court granted judgment to petitioner on all of respondents' claims "because Plaintiffs have failed to show cause why their claims are not preempted under this Court's ruling in *Glynn*." App. 152a. The court held that claims that petitioner should have added a warning to the Warnings and Precautions section were preempted because the court had "already considered and rejected" respondents' arguments in *Glynn*. App. 150a. Respondents also argued that petitioner should have warned of

atypical femoral fractures in the Adverse Reactions section before June 2009. The court did not find that theory preempted but dismissed it as "illogical." App. 146a-147a. The court also concluded, without citing any of the complaints, that the theory was not pleaded in any of the more than 500 complaints. App. 147a. As to the non-failure-to-warn claims, the court concluded on the basis of a single allegation in a single complaint that all respondents' non-failure-to-warn claims were "merely disguised failure to warn causes of action" and were therefore preempted. App. 142a.

The Third Circuit vacated and remanded. The Third Circuit began by noting that this Court's *Levine* decision provided the governing framework. Under that decision, failure-to-warn claims are preempted only "when there is 'clear evidence' that the FDA would not have approved the warning that a plaintiff claims was necessary." App. 30a-31a. Citing cases from this Court using "clear evidence" interchangeably with "clear and convincing evidence," the Third Circuit concluded that *Levine* set forth a standard of proof for the facts underlying the preemption analysis. Under that standard, the inquiry is whether "it is highly probable that the FDA would not have approved a change to the drug's label." App. 37a.

Closely scrutinizing the factual record, the Third Circuit concluded that factual disputes existed regarding whether the FDA would have rejected a properly worded atypical femoral fracture warning in the Warnings and Precautions section. App. 67a-68a. The Third Circuit posited that, while the FDA's rejection of proposed warning language could support the inference that the FDA would have rejected any warning, the FDA's repeated objections to proposed

"stress fracture" language supported the opposite inference that the FDA would have approved a properly worded warning about atypical femoral fractures. App. 5a, 59a-68a. The Third Circuit noted that petitioner's reliance on Ms. Merritt's memorandum as its best piece of evidence raised numerous factual disputes regarding the credibility of Ms. Merritt and the intentions of Dr. Monroe. App. 49a n.125. Citing this Court's decision in *Boyle v. United Technologies Corp.*, 487 U.S. 500 (1988), which held that "whether the facts establish the conditions for [a preemption] defense is a question for the jury," *id.* at 514, the Third Circuit held that resolution of these factual disputes could not be resolved on summary judgment. App. 42a-55a.

The Third Circuit further held that other district court rulings were also erroneous. It ruled that the district court erred in holding that respondents could not pursue failure-to-warn claims based on the theory that petitioner should have added atypical femoral fractures to the Adverse Reactions section before June 2009. The court of appeals explained that this theory was not preempted because petitioner had presented no evidence it could not have added the warning earlier and that the district court erred in summarily dismissing the theory on the merits. App. 70a-73a. The Third Circuit also held that the district court had erroneously dismissed respondents' non-failure-to-warn claims. App. 74a. The petition does not challenge either of those rulings. *See* Pet. 13 n.1 (Adverse Reactions ruling "not at issue here"). In fact, petitioner fails to acknowledge the non-failure-to-warn claims that the Third Circuit held were erroneously dismissed. Pet. 11.

REASONS FOR DENYING THE PETITION

I. THERE IS NO CIRCUIT COURT CONFLICT, AND LOWER COURTS HAVE FAITHFULLY APPLIED *WYETH V. LEVINE*

Petitioner admits that no circuit split exists regarding the conflict preemption issue presented here. Pet. 14 (arguing that this Court should grant review "even absent any circuit conflict"). Rightly so. Since *Wyeth v. Levine*, 555 U.S. 555 (2009), lower courts have consistently understood and applied the basic framework laid out by this Court: failure-to-warn claims generally are not preempted because they pose no obstacle to Congress's purposes and because federal law expressly allows brand-name drug manufacturers to add a warning to the label. *See id.* at 568-81. The manufacturer can, however, establish a preemption defense if it meets its burden to show "clear evidence that the FDA would not have approved" a label change. *Id.* at 571.[2] No federal court of appeals or state court of last resort has reached a conclusion contrary to the Third Circuit's

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[2] *Compare, e.g.*, *Cerveny v. Aventis, Inc.*, 855 F.3d 1091, 1098-99 (10th Cir. 2017) ("we must apply the 'clear evidence' test set forth in *Levine*," under which claims are preempted if defendant "presented clear evidence that the FDA would have disapproved of the warnings suggested by [plaintiffs]"); *Rheinfrank v. Abbott Labs., Inc.*, 680 F. App'x 369, 385 (6th Cir. 2017) ("'[A] court cannot order a drug company to place on a label a warning if there is "clear evidence" that the FDA would not approve it.'") (quoting *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 873 (7th Cir. 2010)); *and Reckis v. Johnson & Johnson*, 28 N.E.3d 445, 460 (Mass. 2015) (claims preempted if there is "clear evidence that the FDA would not have approved a warning" sought by plaintiffs), *cert. denied*, 136 S. Ct. 896 (2016)), *with* App. 37a ("under *Wyeth*, the factfinder must conclude that it is highly probable that the FDA would not have approved a change to the drug's label" to support a preemption defense).

either on the allocation of decision making between the judge and the jury for factual issues underlying the preemption inquiry or on the standard of proof for preemption under *Levine*.

In the absence of a split, petitioner argues that all lower courts are getting it wrong, contending that "lower courts have defied [this Court's] directive," in a "trend" of decisions that are "quite wrong." Pet. 15. Petitioner claims that the lower courts have erred in two ways: (1) misinterpreting *Levine*, and (2) "gutt[ing]" the impossibility preemption defense to make it "impossible for brand-name drug manufacturers to establish preemption." Pet. 15, 18-19 (capitalization omitted). In both respects, petitioner mischaracterizes the lower court cases. Lower courts have carefully applied *Levine*'s anti-preemption rule and clear-evidence exception to the facts of each case, in ways that have resulted in both approval and rejection of preemption defenses.

First, the petition itself disproves petitioner's argument that lower courts have misinterpreted *Levine*. Petitioner bizarrely claims that lower courts have defied this Court by applying the preemption standard exactly as this Court articulated it, requiring "clear evidence" that the FDA would reject a label change to support a preemption defense. Pet. 19 (citing cases). Petitioner's real argument is that this Court did not mean what it said in *Levine*. But this Court's holding that failure-to-warn claims are not preempted absent clear evidence that it would have been impossible to add a warning was no "offhand, solitary reference," as petitioner argues (at 19); it followed from this Court's lengthy analysis of the federal regulatory scheme, which showed that the "premise" of the Federal Food, Drug, and Cosmetic Act is "that manufacturers, not the FDA, bear primary

responsibility for their drug labeling at all times." *Levine*, 555 U.S. at 579.

Second, the contention (at 18) that lower courts "have made proving impossibility preemption under *Levine* next to impossible" is demonstrably incorrect, disproven by the many lower court cases upholding that defense. *See, e.g.*, *Robinson*, 615 F.3d at 873; *In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 43 (1st Cir. 2015); *Cerveny*, 855 F.3d at 1105; *Rheinfrank*, 680 F. App'x at 385; *Reckis*, 28 N.E.3d at 458 (finding claims partially preempted); *Dobbs v. Wyeth Pharms.*, 797 F. Supp. 2d 1264, 1280 (W.D. Okla. 2011); *In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d 1108, 1120-23 (S.D. Cal. 2015), *appeal pending*, No. 15-56997 (9th Cir.). The outcome of this case resulted from petitioner's own failure of proof, not any barrier to preemption erected by the lower courts.

No reason exists to depart from this Court's general practice of "permitting several courts of appeals to explore" an issue and "waiting for a conflict to develop" before granting review. *United States v. Mendoza*, 464 U.S. 154, 160 (1984). That practice is especially appropriate here because conflict preemption issues continue to percolate in the lower courts. For example, in a pending appeal involving diabetes drugs, *Adams v. Merck Sharp & Dohme Corp.*, No. 15-56997 (9th Cir. argued Oct. 3, 2017), the Ninth Circuit is reviewing the district court's grant of summary judgment to defendants (including petitioner) on preemption grounds. Before oral argument, the court issued an order for the parties to be prepared to address the Third Circuit's decision. Order, *Adams*, No. 15-56997, Dkt. 115 (Sept. 15, 2017). If a later circuit court decision disagrees with the decision

below, the Court can consider taking up the issue then. No circuit split warranted this Court's review when it denied certiorari in *Reckis*, 136 S. Ct. 896 (2016), and petitioner concedes that none has developed since.[3]

II. THE THIRD CIRCUIT'S DECISION WAS CORRECT

The Third Circuit correctly determined that petitioner had not established that the FDA would have rejected "a properly-worded warning" of atypical femoral fractures. App. 5a. The FDA's Complete Response to petitioner's proposed warning cited only one reason for the rejection: language that described incorrectly, and minimized the seriousness of, these fractures by referring to them as "stress fractures." Petitioner's theory — that the FDA issued a false Complete Response and that the real reason was insufficient scientific evidence to support any warning — hinged primarily on an ambiguous, self-serving

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[3] *Amici* argue that lower courts are "sharply divided" and "have reached conflicting outcomes on virtually identical regulatory records." PLAC/Chamber Br. 6. This Court should not grant certiorari based on a supposed split identified by *amici* that petitioner concedes does not exist. In any event, *amici* are incorrect. Application of the *Levine* standard is fact-specific, hinging on the drug at issue, the evidence of causation, the FDA's regulatory actions with respect to the drug, and the nature of the plaintiff's legal theories. *See Reckis*, 28 N.E.3d at 457; *Cerveny*, 855 F.3d at 1104. *Amici*'s discussion of the case law (at 9-12) does not show a split warranting this Court's review, but instead reveals courts applying the same legal standard to different facts and legal claims and coming to different results based on the specific circumstances of each case. Moreover, the only so-called splits identified by *amici* involve purported conflicts between *other* decisions. *Amici* point to no decision that conflicts with *this* decision, making this case a poor vehicle to address the issues raised in those other cases.

memorandum by petitioner's employee of a telephone call with an FDA official. Moreover, the FDA *mandated* a proper warning less than 18 months after rejecting petitioner's inaccurate and misleading proposed warning, so it is undisputed that sufficient scientific evidence exists that Fosamax causes atypical femoral fractures to justify a warning. In light of the weakness of petitioner's evidence, the Third Circuit was charitable to petitioner by allowing further proceedings on the preemption defense rather than rejecting it outright.

Petitioner argues for a sweeping rule that, when the FDA rejects *any* proposed warning relating to *any* medical risk, *all* failure-to-warn claims regarding *all* arguably similar risks are preempted, even if the FDA explains that it rejected the warning because the manufacturer's description of the risk was inaccurate and misleading. Pet. 29-30. According to petitioner, it is the FDA's obligation to propose specific warning language, and, in the absence of the FDA mandating a warning, claims that the manufacturer should have added a warning are preempted. Pet. 24. That argument ignores *Levine*'s fundamental teaching that, under federal law, "the manufacturer bears responsibility for the content of its label at all times." 555 U.S. at 570-71.

A. The Third Circuit Correctly Determined That Factual Disputes Existed Regarding Whether The FDA Would Have Rejected A Properly Worded Femur-Fracture Warning

1. The Third Circuit correctly denied summary judgment to petitioner because petitioner failed to proffer clear evidence that the FDA would have rejected a properly worded warning of atypical femoral fractures. There is no dispute that reason-

able evidence exists that Fosamax causes atypical femoral fractures; petitioner agreed as such when it added an atypical femoral fracture warning to the Warnings and Precautions section in January 2011. App. 23a; C.A.App. 1070.

There is ample evidence that petitioner could have added an atypical femoral fracture warning much earlier than that. By 2002, the proliferation of previously rare atypical femoral fractures among Fosamax patients was so extreme that leading orthopedic surgeons began to call them "Fosamax Fracture[s]." C.A.App. 875-76, 1254, 1261. Surveying the scholarly literature and petitioner's adverse event reports, respondents' experts (whose admissibility and qualifications were not challenged) opined that sufficient evidence existed to justify a warning by 2005, if not sooner. C.A.App. 878, 1015. And the FDA stated in 2008 that it was "concerned" about the relationship between bisphosphonates and atypical femoral fractures. C.A.App. 1145.

Petitioner's preemption defense is based on the FDA's rejection of proposed language to warn of "stress fractures." App. 15a-16a (proposed language). But the FDA's "Complete Response" letter explained that the rejection was because "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." App. 18a; C.A.App. 1500.

In its Complete Response, the FDA was required by its own regulations to "describe *all* of the specific deficiencies that the agency has identified in an application." 21 C.F.R. § 314.110(a)(1) (emphasis added). Yet the Complete Response said nothing regarding what petitioner contended was the real reason for the rejection: a supposed deficiency in

the scientific evidence that Fosamax causes atypical femoral fractures. App. 59a.[4] Petitioner repeatedly (but erroneously) contends that denying preemption would require "conjecture," "speculation," or "psychoanalysis" about "some 'hypothetical' reason" that the FDA rejected petitioner's proposed language. Pet. i, 2, 14, 23, 25, 28, 29, 30. The FDA told petitioner exactly why it rejected the language in its official Complete Response. Petitioner just does not like the answer.

If there were any doubt that the FDA disapproved of petitioner's inaccurate and misleading conflation of atypical femoral fractures with stress fractures, that doubt was dispelled the next year. In 2010, after the FDA mandated a warning of atypical femoral fractures, petitioner again proposed language referring to the fractures as stress fractures. App. 22a. The FDA struck every instance of the term "stress fracture" from petitioner's proposed language, explaining that "the term 'stress fracture' was considered and was not accepted" because, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use." App. 22a-23a; C.A.App. 1540, 1557. One need only glance at a gruesome x-ray of someone who has suffered an atypical femoral fracture, C.A.App. 1226, to understand that the term "stress fracture" does not adequately convey the risk to physicians or patients.

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[4] To the contrary, the FDA approved an atypical femoral fracture warning in the Adverse Reactions section, C.A.App. 1500, which required the FDA to conclude there was "some basis to believe there is a causal relationship between" Fosamax and atypical femoral fractures. 21 C.F.R. § 201.57(c)(7).

2. Petitioner argued that the real reason for the FDA's rejection was one nowhere stated in the Complete Response — that scientific evidence of causal association was insufficient to justify any warning. App. 59a. This argument depends on the premise that the FDA violated its own regulations and submitted a misleading Complete Response. The evidence put forward by petitioner to support this theory was at best speculative.

As an initial matter, petitioner distorts the record by misleadingly citing the Third Circuit's rehash of petitioner's legal arguments as a representation of the undisputed facts. *See* Pet. 24 (citing App. 59a-61a). The Third Circuit summarized both sides' glosses on the evidence, *see* App. 59a-62a (petitioner); App. 63a-67a (respondents), before concluding that, based on the evidence, a reasonable factfinder could find for either side, App. 67a-68a. Contrary to petitioner's representation (at 24), the Third Circuit never characterized as "bizarre" the idea that the FDA would have accepted a properly worded atypical femoral fracture warning after rejecting an inaccurate and misleading warning. In fact, the Third Circuit held that "Plaintiffs have produced sufficient evidence for a reasonable jury to conclude that the FDA would have approved a properly-worded warning about the risk of thigh fractures." App. 5a.

Petitioner stated below that its "single best piece of evidence" for its theory was a memorandum by petitioner's employee, Ms. Merritt, of a telephone conversation she had with Dr. Monroe, the FDA official who wrote the Complete Response. App. 49a n.125; C.A.App. 1970; *see* Pet. i, 9 (quoting this memorandum). As the Third Circuit correctly noted, a decisionmaker would need to resolve a host of factual

disputes to "gauge the import" of the memorandum, including to:

> (1) make a credibility determination regarding the Merck employee who drafted the notes; (2) determine the veracity and accuracy of the notes; (3) determine the semantic meaning of Dr. Monroe's statements; (4) infer Dr. Monroe's intent and state of mind when making the statements; and (5) weigh that inference against whatever competing inferences can be drawn from Dr. Monroe's subsequent letter rejecting Merck's proposed warning.

App. 49a n.125. These factual issues precluded the grant of summary judgment to petitioner.

Another document relied on heavily by petitioner is the FDA's email to petitioner stating it would like to "work with . . . [petitioner] to decide on language for a W&P [Warnings and Precautions] atypical fracture language, if it is warranted." C.A.App. 1498; *see* Pet. 9, 24 (quoting this document). That document in fact supports respondents. It shows that the FDA wanted petitioner to come forward with alternative warning language and that the agency was open to approving such language. If, as petitioner contends, the FDA had come to a definitive conclusion that it would reject any atypical femoral fracture warning because of insufficient scientific evidence, that outreach would have been illogical.

In sum, the evidence shows that the FDA would have welcomed a properly worded warning about atypical femoral fractures. Petitioner fell far short of meeting its burden on summary judgment to show clear evidence that the FDA would have rejected such a warning.

B. Petitioner's Arguments Are Inconsistent With This Court's Precedents

The Third Circuit faithfully followed *Levine*. Petitioner's attacks on the decision below are actually attacks on *Levine*, but *Levine* was correctly decided and forecloses petitioner's arguments.

1. Petitioner asks for a bright-line rule that *any* FDA rejection of proposed warning language relating to a medical risk "should suffice — as a matter of law — to preempt state tort liability" for all failure-to-warn claims relating to such a risk. Pet. 30. As a threshold matter, this case provides no opportunity to adopt such a rule because the warning that petitioner proposed and the FDA rejected related to a different risk (stress fractures) than respondents experienced (atypical femoral fractures).

In addition, petitioner's theory ignores the reality that, when the FDA rejects an inaccurate and misleading warning and specifically cites the inaccurate and misleading nature of the warning in its official rejection letter, the FDA would not necessarily reject a properly worded warning of the actual medical risk at issue. As *Levine* noted, a failure-to-warn claim requires showing only that the existing "warning was insufficient." 555 U.S. at 565. Thus, a preemption defense requires "clear evidence that the FDA would not have approved a change to [a drug's] label," *id.* at 571, not just evidence that a specific, misleading formulation of a different warning had been rejected. To adopt petitioner's bright-line rule would deprive the FDA of flexibility to do just what it did here: reject an inaccurate and misleading warning and invite the manufacturer to submit an appropriate warning.

2. Petitioner contends that the fact that the FDA did not immediately *mandate* alternative warning

language means that it would have *rejected* any alternative language proposed by petitioner. Pet. 24. According to petitioner, if there is sufficient scientific evidence to support a warning, it is the FDA's "statutory obligation[]" to mandate such language, so failure-to-warn claims should be preempted absent such a mandate. Pet. 24, 29. That argument misreads the federal drug laws and ignores the central lesson of *Levine*.

Petitioner is incorrect to assert that the FDA has a "statutory obligation[]" to mandate a warning whenever the regulatory standard for a warning is satisfied. Pet. 24; *see also* Pet. 13. The decision whether to mandate such a change is wholly discretionary, hinging on whether the "Secretary [of Health and Human Services] believes" that a label should be changed. 21 U.S.C. § 355(*o*)(4)(A).[5] Moreover, when Congress empowered the FDA to mandate warnings, "it adopted a rule of construction to make it clear that manufacturers remain responsible for updating their labels." *Levine*, 555 U.S. at 567-68.

Thus, the Third Circuit correctly followed this Court's holding that, "[a]s a matter of law, . . . the burden and the responsibility to correct a drug label rests with the manufacturer, not the FDA." App. 67a & n.162 (citing *Levine*, 555 U.S. at 570-71; 21 U.S.C.

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[5] According to FDA guidance, "FDA does not anticipate that all labeling changes that may be related to safety will be required and reviewed under [21 U.S.C. § 355(*o*)(4)]. For other labeling changes, application holders may continue to submit labeling supplements using standard procedures," including the CBE regulation. FDA, *Guidance for Industry Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* 5-6 (July 2013), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf.

§ 355(o)(4)(I)). "Once the FDA rejected [petitioner's] proposal, the ball was back in [petitioner's] court to submit a revised, corrected proposal," App. 67a, particularly because the FDA repeatedly invited petitioner to do so. *See supra* p. 8. The record therefore supported the inference "that it was [petitioner's] failure to re-submit a revised CBE or PAS without stress-fracture language, rather than the FDA's supposedly intransigent stance on the science, that prevented the FDA from approving a label change." App. 67a.

3. Contrary to petitioner's argument (at 25-28), the Third Circuit faithfully interpreted *Levine* in holding that the "clear evidence" standard imposed a heightened standard of proof akin to the "clear and convincing evidence" standard. App. 33a-37a. As the Third Circuit noted, this Court has traditionally used the phrase "clear evidence" as equivalent to "clear and convincing evidence," a standard of proof higher than "mere preponderance of evidence." *E.g.*, *Oriel v. Russell*, 278 U.S. 358, 362-63 (1929); *Ramsey v. United Mine Workers*, 401 U.S. 302, 307-09, 311 (1971) (interpreting statute requiring "clear proof" as requiring "clear and convincing evidence"); *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 97, 113-14 (2011) (equating Federal Circuit's "clear evidence" standard for patent invalidity with a "clear-and-convincing-evidence standard").

Petitioner contends (at 27) that this Court imposes a clear-and-convincing-evidence standard only "for good reason." But the majority and concurring opinions in *Levine* identified multiple good reasons for a heightened standard of proof. As the majority explained, because "a central premise of federal drug regulation" is "that the manufacturer bears responsi-

bility for the content of its label at all times," it is "difficult to accept" the idea that the FDA would punish a manufacturer "for strengthening a warning." 555 U.S. at 570-71. As Justice Thomas noted, preemption of failure-to-warn claims against brand-name drug manufacturers goes beyond traditional impossibility preemption because the CBE regulation makes it "physically possible" for a manufacturer "to comply with a state-law requirement to provide stronger warnings . . . while continuing to market [a drug] in compliance with federal law." *Id.* at 591-92 (Thomas, J., concurring in the judgment). Because such preemption arguments rest on speculation that a federal agency *might have* blocked a manufacturer if it complied with state law (rather than a contention that compliance with state law was impossible in the first instance), this Court properly imposed a heightened burden to advance "clear evidence" to support such a defense.

In any event, application of a preponderance standard would have made no difference in the outcome of this case. That is because, regardless of the standard of proof, "[s]ummary judgment is appropriate only if 'the movant shows that there is no genuine issue as to any material fact and the movant is entitled to judgment as a matter of law.' In making that determination, a court must view the evidence 'in the light most favorable to the opposing party.'" *Tolan v. Cotton*, 134 S. Ct. 1861, 1866 (2014) (per curiam) (quoting Fed. R. Civ. P. 56(a); *Adickes v. S.H. Kress & Co.*, 398 U.S. 144, 157 (1970)). Given the summary-judgment standard, the weakness of petitioner's evidence, and the factual disputes raised by petitioner's reliance on Ms. Merritt's memorandum, petitioner could not have won summary judgment under any standard of proof.

4. Nor was it error, under the circumstances of this case, to hold that the preemption inquiry involved disputed factual issues for the factfinder. The Third Circuit concluded that, while "*most* preemption cases present purely legal questions[,] . . . it is equally clear that preemption can be, and sometimes must be, a fact question for the jury." App. 42a. That conclusion was consistent with and compelled by this Court's holding in *Boyle v. United Technologies Corp.*, 487 U.S. 500 (1988), that, in the context of a government contractor preemption defense, "whether the facts establish the conditions for the defense is a question for the jury." *Id.* at 514.

Here, petitioner's efforts to contradict the official regulatory record with self-serving hearsay evidence of informal communications with the FDA provided no basis for granting summary judgment in petitioner's favor. The official regulatory record did not support petitioner's preemption defense, because the FDA's Complete Response listed the inaccurate and misleading stress-fracture language as the only deficiency in petitioner's proposed warning application. C.A.App. 1500-01. However, petitioner supported its preemption defense by citing a memorandum written by one of petitioner's employees regarding a telephone conversation she had with the same FDA official who wrote the Complete Response, which (under petitioner's reading of the memorandum) supported a contradictory inference about why the FDA rejected petitioner's proposed warning. As the Third Circuit concluded, assessing such evidence requires "precisely the types of personal evaluations and weight-of-the-evidence assessments" that are typically reserved for the trier of fact. App. 49a n.125.

III. THIS CASE PRESENTS A POOR VEHICLE TO ADDRESS THE SCOPE OF CONFLICT PREEMPTION

Even if the Court wished to address the scope of conflict preemption of failure-to-warn claims, this case is a poor vehicle to do so in many respects.

1. This case does not implicate the policy concerns that petitioner and *amici* contend warrant review. Petitioner asserts that review is necessary because state tort law can "undermine[] the FDA's expert judgment" about what warnings are necessary, leading to overwarning where "the FDA would have made" a different "policy decision" from the jury. Pet. 31-32. Similarly, *amici* warn that state tort lawsuits can upset the "balance" of what warnings should be included on the label and lead to "warnings that are not grounded in science." PhRMA Br. 6.

At the outset, this Court rejected those policy arguments in *Levine*. There, as here, the drug manufacturer contended that FDA regulation "establishes both a floor and a ceiling for drug regulation." 555 U.S. at 573. This Court disagreed, explaining that "all evidence of Congress' purposes is to the contrary." *Id.* at 574. The policy arguments of petitioner and its *amici* cannot be reconciled with this Court's rejection of the same arguments in *Levine*.

In any event, petitioner's and *amici*'s policy concerns are entirely inapplicable here, because the FDA has in fact determined that Fosamax's label should include a warning about atypical femoral fractures. In October 2010, the FDA required all bisphosphonate manufacturers to add an atypical femoral fracture warning, based on its scientific judgment that "'these atypical fractures may be related to long-term . . . bisphosphonate use.'" App.

20a (quoting C.A.App. 1118) (alteration in original). Accordingly, in January 2011, petitioner added a warning of "Atypical Subtrochanteric and Diaphyseal Femoral Fractures" to the Fosamax label. C.A.App. 1070-71. Thus, the FDA has already made an "expert judgment" and a "policy decision" that an atypical femoral fracture warning *is* appropriate. In agreeing to add an atypical femoral fracture warning (rather than challenging the FDA's scientific determination), petitioner has forfeited any argument that such a warning is "not grounded in science."

These cases are thus different from the typical failure-to-warn case where the parties dispute the necessity of a warning. Here, petitioner and the FDA *agree* with respondents that a warning is necessary. These cases cannot result in a situation in which the manufacturer would need to add a warning to avoid liability, because that warning was added to the label more than six years ago (albeit too late to prevent respondents' injuries). Accordingly, any concerns that state tort lawsuits encourage over-warning or upset the FDA's judgments are wholly inapplicable here.

2. This case is also a poor vehicle because the district court's violations of respondents' procedural rights may prevent. and will at least hinder, the Court from considering the question presented. As noted above, the district court held that respondents' claims were preempted on the basis of its preemption opinion in *Glynn v. Merck Sharp & Dohme Corp.*, a case to which *none* of the respondents was a party. On the basis of that opinion, the court ordered every respondent to show cause why their claims were not preempted, giving each respondent just 45 days to summon evidence in opposition to preemption. C.A.App. 769. Although respondents did the best they

could under the circumstances, they argued to the court that it would be procedurally improper to apply the ruling in the *Glynn* case (to which they were not parties) against them through a show-cause procedure that did not give them an adequate opportunity to develop evidence. Dist. Ct. Dkt. 2995-3.

In dismissing respondents' claims, the district court held that, on the basis of the *Glynn* ruling, "the burden [wa]s therefore shifted to [respondents]" to disprove preemption, App. 132a, in violation of the controlling summary-judgment standard. The court then applied its *Glynn* ruling to respondents, with minimal additional analysis. App. 150a-152a. Respondents argued on appeal that "[i]t was procedurally improper for the district court to shift the burden to [respondents] as a result of the preemption opinion in *Glynn*." Plaintiffs-Appellants C.A. Br. 67. Although the Third Circuit did not need to reach respondents' procedural objections because it held that petitioner was not entitled to summary judgment, it did note that "a deeper problem lurking" in the district court's analysis was its inability to acknowledge that "[a] mass tort MDL is not a class action," but "is a collection of separate lawsuits that are coordinated for pretrial proceedings — and *only* pretrial proceedings," and that "the District Court's understandable desire to streamline proceedings cannot override the Plaintiffs' basic trial rights." App. 72a-73a.

If this Court grants certiorari, respondents may raise the district court's violations of their procedural rights as an alternative and independent ground for affirming the Third Circuit's ruling that petitioner was not entitled to summary judgment. *See United States v. Tinklenberg*, 563 U.S. 647, 661-63 (2011) (affirming based on "alternative grounds"). Should this

Court agree with respondents' procedural arguments, it will not be able to reach the question presented by the petition.

At the very least, the district court's cursory procedure led to an underdeveloped factual record. For example, petitioner's "single best piece of evidence," App. 49a n.125, was Ms. Merritt's memorandum purporting to summarize her telephone conversation with Dr. Monroe. But Ms. Merritt has not been deposed. Moreover, the district court's decision to dismiss more than 500 lawsuits in one fell swoop with no analysis of the specific circumstances of any case may hinder this Court's review, should this Court determine that plaintiff-specific facts (such as the timing of respondents' injuries or the state law that applies to their claims) are relevant to the analysis. If this Court wishes to consider the scope of conflict preemption, it should do so in the context of a fully developed factual record, not in a circumstance in which the district court's unorthodox use of a show-cause order forced the parties to scramble to gather evidence in 45 days.

3. Even if petitioner prevails on the question presented, it will have limited impact (and may have no impact) on these cases. Petitioner concedes (albeit buried in a footnote) that respondents' failure-to-warn claims *are not preempted* insofar as they are based on the theory that petitioner should have added a warning of atypical femoral fractures to the Adverse Reactions section of the label before June 2009. Pet. 13 n.1.[6] Thus, even if this Court rules

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[6] As the Third Circuit recognized, even respondents injured after June 2009 can assert that their injuries were caused by Fosamax usage before the Adverse Reactions label change. App. 70a n.165.

for petitioner, respondents' failure-to-warn claims will survive. They would merely be narrowed from two sections of the Fosamax label (Adverse Reactions, and Warnings and Precautions) to one (Adverse Reactions).[7]

Moreover, petitioner does not challenge the Third Circuit's separate holding that none of respondents' non-failure-to-warn claims are preempted. App. 74a. As the Third Circuit noted, many of respondents' complaints include claims for design defect, negligence, fraud, breach of warranty, deceptive trade practices, and other claims. App. 24a.[8] Petitioner does not even mention these claims in its petition. These claims, like the Adverse Reactions aspect of the failure-to-warn claims, will survive regardless of this Court's ruling.

Even as to the Warnings and Precautions aspect of respondents' failure-to-warn claims, the Third Circuit did not reject petitioner's preemption defense but merely denied summary judgment. App. 67a-68a. Nothing justifies the extraordinary step of granting review in this interlocutory posture. Petitioner may yet prevail on remand, either on its preemption defense or on some other ground. And petitioner has identified nothing that would prevent this Court

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[7] Petitioner's description (at 13 n.1) of the Adverse Reactions theory as a "distinct failure-to-warn claim" is inaccurate. As the Third Circuit explained, respondents "alleg[ed] generally that the Fosamax label did not adequately warn patients and doctors of the fracture risk," and these general allegations encompassed both "the Warnings and Precautions theory" and "the Adverse Reactions theory." App. 71a.

[8] *See* C.A.App. 2252-80, 2304-06, 2311-15, 2331-33, 2335-47 (examples of non-failure-to-warn claims in respondents' complaints).

from reviewing the preemption issue on appeal from a final judgment, in the event petitioner does not prevail.

4. Finally, petitioner's argument (at 34) that this case provides "an excellent vehicle for putting another stake in the ground . . . to illustrate facts that *prove* preemption" has no merit. For several reasons described in greater detail above, petitioner's preemption evidence is weak:

(1) It is undisputed that sufficient scientific evidence exists to justify an atypical femoral fracture warning.

(2) The FDA mandated an atypical femoral fracture warning many years ago.

(3) The first time petitioner proposed any warning, the FDA approved a warning on one section of the Fosamax label.

(4) The FDA's only reason given in its Complete Response for rejecting the proposed language on the other section of the Fosamax label was that petitioner's language mischaracterized the risk, and the FDA later confirmed that this proposed language "contradict[ed] the seriousness" of the risk and would confuse physicians by making serious atypical femoral fractures seem like a "minor fracture."

(5) Petitioner's "single best piece of evidence" to support preemption was a self-serving memorandum written by one of petitioner's employees purporting to describe a phone call she had with an FDA official.

If the Court wants to review a case involving unassailable evidence of preemption in order to plant a "stake in the ground," it should look elsewhere.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted,

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No. 17-290

IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,

Petitioner,

v.

DORIS ALBRECHT, ET AL.,

Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Third Circuit

REPLY IN SUPPORT OF PETITION FOR A WRIT OF CERTIORARI

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The decision below guts the preemption defense recognized in *Wyeth v. Levine*, 555 U.S. 555 (2009). Merck told the FDA everything it knew about the possible link between Fosamax and atypical femur fractures. It proposed to change the label to warn of that risk. But the FDA rejected that proposal and cast doubt on the underlying science. The Third Circuit *accepted all of this*, yet still let Respondents' failure-to-warn claims proceed. Absent a "smoking gun," the court reasoned, a lay jury must muse about whether the FDA—neglecting its *own* legal duties—rejected Merck's proposal exclusively for semantic reasons and thus might conceivably have approved an alternative warning satisfying state law.

Under *Levine*, the FDA's rejection of a proposed warning is preemptive. *Id.* at 571-72. And, under *PLIVA, Inc. v. Mensing*, "conjecture[]" does not "suffice" to defeat the defense. 564 U.S. 604, 621 (2011). Accordingly, if a manufacturer shares its data on a risk, proposes to warn of it, and is rebuffed, the case is over. There is no room for a jury to deconstruct the FDA's decision or speculate about an infinite array of counterfactuals. Nonetheless, courts have—through a line of decisions culminating in the one below—made it all but impossible for drug manufacturers to navigate FDA oversight while still protecting themselves against massive tort liability.

Respondents barely dispute Merck's view of the law. Instead, they purport to reconcile it with the decision below, by mischaracterizing the record and misrepresenting the court's rationale. But the Third Circuit understood the relevant facts—that Merck proposed a warning about the risk at issue; that the FDA said no, with no wriggle room; and that the

FDA expressed skepticism on the science both before and for 18 months after the rejection. Its legal holding—based on an artificially heightened burden of proof, deference to juries on matters of regulatory process, and a skewed understanding of *Levine*—was that *not even this* suffices to trigger preemption. Respondents cannot hide from those legal errors.

Respondents' other ground for denying review is their assertion that this case is a poor vehicle. Quite the opposite. The Third Circuit's aggressive holding turns the FDA's authority over to 500-plus juries in the underlying MDL alone, not to mention its systemic effect on this important area of law. As for Respondents' half-hearted "alternative ground" to affirm, the court below did not pass upon it, so it is no excuse to shield from review what the court *did* decide. And Merck's agreement on the need for a warning simply highlights the inequity of the Third Circuit's rule: Even a manufacturer doing its best to warn the public can be stymied by federal regulation and then hit with enormous state-law liability.

I. RESPONDENTS DEFEND THE THIRD CIRCUIT'S RULING ONLY BY MISCHARACTERIZING IT

A. It is untenable to hold manufacturers liable for failure-to-warn under state law even when they (i) sought approval to issue a warning and (ii) were told "no" by a federal regulator that (iii) viewed the science differently. Pet.28-30. Respondents do not appear to disagree with that legal rule. They instead suggest, through selective and misleading accounts of the record, that the Third Circuit did not hold otherwise. But the court below was very clear: It denied summary judgment to Merck *despite* these facts, not by *disputing* them.

First, Respondents insist that Merck "never proposed" warning about the relevant risk ("atypical femoral fractures"), but "only about a different risk—minor stress fractures." Opp.1-2; *see also* Opp.i, 18.

That incredible revisionism was *not* a basis of the decision below. Rather, the Third Circuit recognized that Merck had informed the FDA about "possible connections between long-term bisphosphonate use and *atypical femoral fractures*," and had proposed a warning about "[l]ow-energy *fractures* of the subtrochanteric and proximal *femoral shaft*." Pet.App.13a, 15a (emphases added). The FDA's response letter, likewise, described Merck's proposed warning as concerning "low-energy fractures at the subtrochanteric region of the femoral shaft." C.A.App.1500. Given all this, it is no wonder that the court below readily acknowledged that Merck's proposal "address[ed] atypical femoral fractures," Pet.App.15a, not "minor stress fractures."

Ignoring these facts, Respondents note that Merck's proposal alternatively described the fractures in question as "stress fractures." Opp.7. So what? Merck's proposal was *titled* "**Low-Energy Femoral Shaft Fracture**," and it grew out of a back-and-forth with the agency that centered on such fractures. Pet.App.13a-15a. Moreover, these femoral fractures *are* a particular example of stress fracture, C.A.App.A2013, and even if the FDA found that language confusing, there was no doubt that Merck's warning related to the very risk at issue in these cases, as the court below acknowledged.

Second, Respondents claim that the FDA merely asked Merck to *revise* its proposed warning, and that Merck "rebuffed" its "repeated entreaties." Opp.8.

This rewriting of history is worse than the last. Respondents selectively quote an FDA letter that offered to "work with" Merck on "atypical fracture language, if it is warranted," Pet.App.17a-18a—but they ignore the part of the letter that asked Merck to "*hold off*" on adding any fracture-related language so that the agency could "close out" Merck's PAS and *then* investigate—with Merck and the FDA's Office of Surveillance and Epidemiology—whether a warning was "warranted," C.A.App.A1498 (emphasis added). Far from inviting Merck to *revise* its proposal, the FDA asked Merck to *drop* it. And, again, the court below so recognized, recounting how the FDA firmly stated that it was "not prepared to include language about low-energy femoral fractures in the Warnings and Precautions section of the label." Pet.App.17a.

Respondents retort that the complete response letter "invited [Merck] to 'resubmit' its application." Opp.8. But the word "resubmit" appears only in a boilerplate recitation of regulatory options: "Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110." C.A.App.A1501. This did not "entreat" Merck to do anything, Opp.8, and the Third Circuit never mentioned it, much less relied on it. Had the FDA wanted Merck to rephrase, it was obligated to say so: "When possible, a complete response letter will recommend actions that the applicant might take to place the application ... in condition for approval." 21 C.F.R. § 314.100(a)(4).

Finally, Respondents insist that the FDA never articulated any doubts about the science, and instead expressly rejected Merck's proposal merely based on minor wording quibbles. Opp.18-20.

Once again, however, the Third Circuit acknowledged the "force" of the undisputed facts. Pet.App.62a. Among other things:

- Before denying Merck's request, the FDA asked Merck to "hold off" pending further research by agency scientists into whether a warning was "warranted," Pet.App.17a-18a;
- After denying Merck's request, the FDA announced that, as the data had "not shown a clear connection between bisphosphonate use and ... femur fractures," it would "gather additional information" through an "outside expert task force," Pet.App.19a; and
- After that task report issued a report, the FDA declared it was "confident that atypical femur fractures are potentially more closely related" to bisphosphonate use than it "previously had evidence for," and required manufacturers to add warnings, Pet.App.21a.

Respondents largely ignore this evidence, instead declaring (*e.g.*, Opp.2, 16-17, 20-21, 32) that Merck's case "hinged" on hearsay notes of a call on which the FDA said the "conflicting nature of the literature d[id] not provide a clear path forward," Pet.App.17a. Merck's counsel's identification of those notes at oral argument hardly makes them Merck's *only* evidence. In fact, the entire above timeline—with which those notes are consistent—proves the point.

Respondents further assert that the FDA *must* have rejected the proposal solely based on language quibbles, as its complete response letter mentioned stress-fracture language yet allegedly did not quarrel with the underlying science. Opp.16, 18-19. Again,

however, Respondents just ignore the evidence they dislike. The response letter provided "*reasons*" for the rejection—plural—and its *very first* was that Merck's proffered "*justification* for the proposed **PRECAUTIONS** section language is inadequate." Pet.App.18a (emphases added). That is, the agency was not persuaded by the scientific case that must justify any label change. Whatever issues it had with the term "stress fracture"—identified *separately* in the letter's *next* sentence—scientific doubt was an independent ground for rejection.

This understanding of the response letter is the only one that comports with the FDA's other actions (such as asking Merck to "hold off," and working with the task force) and the only one reconcilable with the FDA's own legal duties. The FDA *must* "initiate discussions to reach agreement on ... the content[]" of "label changes" if it "becomes aware of new safety information" justifying such a change, 21 U.S.C. § 355(o)(4)(A), (C)—a duty that Respondents neither dispute nor address. The FDA indisputably was aware of all of the safety information related to this issue. Thus, if the FDA believed that a warning was scientifically justified, it was obligated to work with Merck to craft one. That is precisely what the FDA did 18 months later, when it deleted "every instance" of use of the term "stress fractures" from Merck's post-task force proposal. Pet.App.22a. Its failure to do the same in 2009 belies Respondents' narrative.

B. Respondents try to downplay the reach of the decision below not only by muddying the facts on the substantive preemption issue, but also by misstating the court's legal holdings on two related points.

First, while Respondents admit that the Third Circuit decision requires manufacturers to prove preemption by clear and convincing evidence, Opp.24, they maintain that the "application of a preponderance standard would have made no difference" here, because of the supposed "weakness of [Merck's] evidence," Opp.25. Even setting aside their grossly misleading description of that evidence, *see supra* pp. 3-6, that is wrong. The Third Circuit *itself* tied its conclusion to its clear-and-convincing-evidence standard. It acknowledged Merck's strong case, *e.g.*, Pet.App.62a, but held that, because the standard of proof is "[c]rucial[]," Merck had to prove that no rational juror could find the odds of rejection "something less than highly probable," Pet.App.58a; *see also* Pet.App.55a (demanding a "smoking gun"). Merck fell short solely because it could not meet that "heightened standard." Pet.App.68a.[1]

Second, Respondents suggest that the Third Circuit's other crucial legal conclusion—that a *jury* must determine whether the FDA would have approved the requested warning—was limited to the "circumstances of this case" because Merck sought to

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[1] Respondents only halfheartedly defend the circuit court's standard of proof, Opp.24-25, and Merck already distinguished the authority on which they rely, Pet.25-28. Respondents' only new case applied a *statute* dictating a "clear proof" test, *Ramsey v. United Mine Workers of Am.*, 401 U.S. 302, 309 (1971), in no way supporting a judge-made heightened-proof rule here. As for the notion that such a standard is appropriate because the preemption defense rests on "speculation," that misses the point. Absent a congressional directive, cases seeking money damages simply are not important enough to justify burdening one side with more of the risk of error, regardless of the *source* of that risk. *See Santosky v. Kramer*, 455 U.S. 745, 755 (1982).

rely on evidence outside the "official regulatory record." Opp.26. Not so. The Third Circuit held, as a *categorical* matter, that "whether the FDA would have rejected a proposed label change is a question of fact that must be answered by a jury." Pet.App.38a; *see id.* at 39a-54a. In doing so, the court rejected not only Merck's view on that issue, but *Respondents'* view that "judicial decisionmaking is required when a preemption determination" includes evaluation of a complete response letter. Pet.App.52a. Under the Third Circuit's remarkable holding, the jury in *all* circumstances presumptively determines the applicability of the legal preemption defense through an "evaluative inference about human behavior," which it should base on "correspondence, agency statements, contemporaneous medical literature, the requirements of the CBE regulation, and whatever intuitions [it] may have about administrative inertia and agency decision-making." Pet.App.54a.[2]

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[2] Again, Respondents' defense of the Third Circuit's rule on the merits is muted at best. The law-soaked question whether the FDA would have approved a particular warning differs significantly from the question whether equipment conformed to government specifications, *see Boyle v. United Techs. Corp.*, 487 U.S. 500, 512-14 (1988). This Court has regularly left such questions for judges, not juries. *See, e.g.*, *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996) (construing disputed terms of art in a patent); *Miller v. Fenton*, 474 U.S. 104 (1985) (whether confession was "voluntary").

II. This Case Remains an Ideal Vehicle for Clarifying the Scope of a Critical Defense

A. This Court's guidance is needed on how to apply what the Third Circuit called *Levine*'s "cryptic," "open-ended" statement about "clear evidence." Pet.App.28a. Respondents insist that this Court should deny review because no square circuit split exists. Opp.13. But this Court has reviewed even one-off erroneous preemption decisions because of the "importance of the ... issue," *Levine*, 555 U.S. at 563. Where, as here, lower courts have gone off-course *en masse*, Pet.18-25, review is even more obviously warranted.

Respondents respond that, in fact, courts uphold preemption defenses on occasion. Opp.15. The cases they cite, however, only highlight the lower courts' stingy application of *Levine*: limiting the defense to scenarios where the FDA rejected a *nearly identical* warning, *expressly* for policy reasons. Pet.20-22; *e.g.*, *Reckis v. Johnson & Johnson*, 28 N.E.3d 445, 458-59 (Mass. 2015) (no preemption for failure to warn of "life-threatening disease," even though FDA rejected warning for "life-threatening diseases, including [three named ones]," because the rejection "could well have" stemmed from the naming of specific diseases).[3] That is obviously not the only situation

[3] Ironically, Respondents also cite a decision, pending on appeal in the Ninth Circuit, where *Respondents' counsel* is seeking reversal *based on the decision below*. Opp.15. They also cite *In re Celexa & Lexapro Marketing & Sales Practices Litigation*, 779 F.3d 34 (1st Cir. 2015), but that decision found preemption because the absence of "newly acquired information" precluded the manufacturer from changing its label unilaterally, not because the FDA would have rejected a change. *Id.* at 41-43.

in which the FDA "would have prevented" the manufacturer from adding a warning, *Levine*, 555 U.S. at 573, and yet lower courts have wrongly made that the bar.

B. Respondents next object that this case would not be a good vehicle to clarify preemption law. But, if anything, their arguments only highlight the need for guidance in this field.

First, Respondents claim that they have *other* claims against Merck that may not be affected by the resolution of this case. Opp.30-32. Actually, most of those are failure-to-warn claims by another name; the district court dismissed them as just derivative (Pet.App.139a-46a); the Third Circuit revived them only because it revived the central failure-to-warn claims (Pet.App.74a). Meanwhile, by virtue of the Third Circuit decision, Merck faces the prospect of more than 500 individual trials at which *different* juries must speculate about whether the FDA would have approved a marginally rephrased warning.

Moreover, this particular MDL aside, Merck and every other pharmaceutical manufacturer must now innovate in the shadow of the Third Circuit's indefensible legal rules. This Court has not hesitated before to grant interlocutory review in such circumstances. *See Mensing*, 564 U.S.at 610-11.

Second, Respondents threaten that they "may"—"may"—"raise the district court's [alleged] violations of their procedural rights" as an alternative ground for affirmance. Opp.29. They admit, however, that the Third Circuit "did not ... reach [their] procedural objections." *Id.* At most, their (non-jurisdictional) complaints are thus a matter for eventual remand.

In any event, the district court's show-cause procedure was perfectly proper. Many courts have followed similar procedures when addressing cross-cutting issues in the MDL context, and the district court gave Respondents chance after chance to develop their arguments. Pet.App.135a-36a.

There is no genuine risk that the record relevant to the preemption issue is "underdeveloped." Opp.30. Respondents cite just one example of an allegedly "missing" fact—deposition testimony from Ms. Merritt, the Merck employee who took the notes of the FDA phone call that Respondents claim are the linchpin of Merck's case. That is specious, both because the notes are hardly central to the outcome, *supra* p. 5, and because Respondents offer no basis to doubt that they accurately recount the call. Plus, given the many opportunities they had to seek this evidence, Respondents' "failure" to do so "is no [one's] fault other than" their own. Pet.App.136a.

Third, Respondents press the strange argument that, because all *now* agree that bisphosphonate labels should warn about atypical femoral fractures, the dangerous policy implications of unrestrained failure-to-warn claims are somehow absent here. Opp.27-28. That simply does not follow. Before the task force report, the FDA did not believe there was enough evidence to warn about atypical femoral fractures. *Supra* pp. 5-6. Respondents seek to upset that expert decision by asking juries to penalize Merck for having failed to warn *during that period*. Indeed, this case highlights the no-good-deed-goes-unpunished nature of the decision below: Merck faces liability even though it *tried* to warn of a developing risk and was rebuffed.

Furthermore, the Third Circuit's decision will create havoc in *other* cases. Its clear-and-convincing-evidence standard will by definition supplant the FDA's judgment with a jury's, defeating preemption even where it is shown (by a preponderance) that the FDA would have rejected a warning. Similarly, the Third Circuit's demand for a "'smoking gun' rejection letter," Pet.App.55a, will produce a wasteful flurry of requests to add alternatively phrased warnings. These are compelling reasons for review that have nothing to do with Fosamax. Of course, if the Court has any doubt about these policy implications, it could solicit the FDA's views.

Finally, Respondents do not dispute the need for another "stake in the ground" to help lower courts, but argue that Merck's "evidence is weak." Opp.32. Repeating this bogus claim does not make it true. If a manufacturer can be liable even after telling the FDA about the risk, proposing an on-point label, and being turned down while the FDA expressed concerns about the science, *Levine*'s preemption defense might as well not exist at all.

CONCLUSION

The petition should be granted.

NOVEMBER 2017

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BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

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QUESTION PRESENTED

Whether a state-law failure-to-warn claim alleging the insufficiency of brand-name drug labeling is preempted by the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.*, when the Food and Drug Administration, after the drug manufacturer provided it with the relevant scientific data, rejected the manufacturer's application to modify its labeling to warn about the risk underlying the tort claim.

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ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

INTEREST OF THE UNITED STATES

This brief is submitted in response to the Court's order inviting the Solicitor General to express the views of the United States. In the view of the United States, the petition for a writ of certiorari should be granted.

STATEMENT

1. This case involves a series of tort claims alleging that petitioner's labeling for its Fosamax drug products insufficiently warned of the drugs' risks. Petitioner has argued, *inter alia*, that many of the failure-to-warn claims are preempted because, in 2009, the Food and Drug Administration (FDA) rejected its attempt to strengthen relevant warnings on that labeling. The regulatory scheme for drug labeling sets the stage for that defense.

a. Congress has charged FDA with ensuring that each "drug is safe for use under the conditions prescribed, recommended, or suggested" in its "labeling."

21 U.S.C. 355(d); *cf.* 21 U.S.C. 352(f) (misbranding). FDA regulations govern the content and format of prescription-drug labeling. See, *e.g.*, 21 C.F.R. 201.56, 201.57; see 21 C.F.R. 201.100(c). Those regulations are intended to organize labeling information to more effectively communicate to healthcare professionals the "information necessary for the safe and effective use of prescription drugs." 71 Fed. Reg. 3922, 3928 (Jan. 24, 2006). Two separate labeling sections now generally required on prescription-drug labeling are relevant here: the Warnings and Precautions section and the Adverse Reactions section. See 21 C.F.R. 201.57(c)(6) and (7).[1]

The Warnings and Precautions section must identify "clinically significant adverse reactions" and certain other safety hazards where "reasonable evidence of a causal association" between the drug and such hazards

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[1] The specific requirements for labeling content and format discussed in the text generally apply to prescription drugs subject to a new drug application (NDA) or efficacy supplement approved on or after June 30, 2001. 21 C.F.R. 201.56(b)(1). The specific labeling requirements for older drug products differ in certain respects. See 21 C.F.R. 201.56(e), 201.80.

This case involves the labeling of three FDA-approved Fosamax products: Fosamax tablets (NDA 20560; approved 1995), Fosamax oral solution (NDA 21575; approved 2003), and Fosamax Plus D tablets (NDA 21762; approved 2005). See C.A. App. A1500; see also FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations* 3-12, 6-14 (38th ed. 2018) (listing Fosamax products). Although the newer labeling requirements discussed in this brief did not apply to all of those products at the time relevant here, no party has suggested that the differences between the two sets of labeling requirements are relevant to this case. The government agrees. This brief therefore follows the path taken by the court of appeals, which based its decision on the newer labeling requirements in Section 201.57(c) without discussing Section 201.80. See Pet. App. 7a-9a & nn.6, 9-10, 16, 51a n.130, 63a-64a nn.154, 156.

exists. 21 C.F.R. 201.57(c)(6); see 73 Fed. Reg. 49,603, 49,604 (Aug. 22, 2008) (stating that a "'preponderance' of evidence" is not required). FDA adopted that causal standard in part to "prevent overwarning" of potential risks, which, if included in the Warnings and Precautions section, could dilute other "more important warnings" or "deter appropriate use" of the drug. 73 Fed. Reg. at 49,605-49,606. FDA thus reserves this section for only a "discrete set" of hazards serious enough to affect prescribing decisions. FDA, *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* 3 (Oct. 2011), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf.[2]

The Adverse Reactions section, by contrast, describes "the overall adverse reaction profile of the drug." 21 C.F.R. 201.57(c)(7). The causal threshold for including an adverse reaction in this section is lower than that for the Warnings and Precautions section: An adverse reaction must be listed if "some basis" exists "to believe there is a causal relationship between the drug and the occurrence of the adverse event." *Ibid.*

b. A brand-name drug "manufacturer bears responsibility for the content of its label[ing] at all times." *Wyeth* v. *Levine*, 555 U.S. 555, 570-571 (2009); see 21 U.S.C. 355(*o*)(4)(I). When new information becomes available about a new risk or a new aspect of a known risk that causes existing labeling to become inadequate,

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[2] The 2011 guidance describes FDA's interpretation of its 2006 labeling regulations, and FDA has informed this Office that the 2011 guidance accurately reflects how FDA treated the Warnings and Precautions section during the period relevant here.

the manufacturer is responsible for pursuing a revision to its labeling. See 21 C.F.R. 201.57(c)(6) (stating that updated warning must be added "as soon as" sufficient causal evidence exists); 21 C.F.R. 201.57(c)(7)(ii)(B) (requiring list of adverse reactions identified in postmarketing experience).[3]

i. After FDA has approved a new drug application (NDA) for a drug, 21 U.S.C. 355(b)(1) and (d), two mechanisms exist for changing a brand-name prescription drug's labeling, both of which require that the manufacturer file a supplemental NDA for FDA approval. First, the sponsor may submit a Changes Being Effected (CBE) supplement for certain labeling changes, which allows the manufacturer immediately to implement its proposed labeling changes upon FDA's receipt of the supplement. 21 C.F.R. 314.70(c)(6) and (iii); see *Wyeth*, 555 U.S. at 571, 573. A CBE supplement may be submitted, *inter alia*, to add or strengthen a warning, precaution, or adverse reaction to reflect "newly acquired information" if "the evidence of a causal association satisfies the [relevant] standard for inclusion in the labeling." 21 C.F.R. 314.70(c)(6)(iii)(A); see 21 C.F.R. 314.3(b) (defining "[n]ewly acquired information"). If FDA later disapproves the supplement, however, it may order the manufacturer to cease distributing the drug with the labeling changes. 21 C.F.R. 314.70(c)(7).

Second, the sponsor may submit a Prior Approval Supplement (PAS) to propose labeling changes, under which FDA approval is required before the changes are made. 21 C.F.R. 314.70(b)(2)(v)(A) and (3). A PAS

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[3] Because a generic drug's labeling generally must track that of its reference listed drug, generic-drug manufacturers cannot independently change such labeling. See, *e.g.*, *Mutual Pharm. Co.* v. *Bartlett*, 570 U.S. 472, 486, 488 (2013).

"must be submitted" for certain types of changes that "include, but are not limited to," certain labeling changes other than those described in Section 314.70(c)(6)(iii) for CBE supplements. 21 C.F.R. 314.70(b)(1), (2), and (v)(A). Historically, FDA has also accepted PAS applications instead of CBE supplements, as occurred in this case, particularly where significant questions exist on whether to revise or how to modify existing drug labeling.[4]

ii. "All procedures and actions that apply to an application" submitted to FDA generally apply "to supplements." 21 C.F.R. 314.71(b) and (c). FDA has accordingly confirmed to this Office that it follows many of the general principles applicable to its review of an NDA when undertaking the more limited task of reviewing supplements that propose safety-related labeling changes. More specifically, FDA communicates with the applicant about "scientific, medical, and procedural issues that arise" in the course of its review. 21 C.F.R. 314.102(a). The "[d]evelopment of final labeling" generally is then "an iterative process between the applicant and FDA" involving a series of communications.[5] If FDA reviewers identify "easily correctable deficiencies" in a supplement,

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[4] Cf. FDA, *Guidance for Industry: Safety Labeling Changes—Implementation of Section 505(o)(4) of the FD&C Act* 7 (July 2013), https://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM250783.pdf.

[5] See Center for Drug Evaluation & Research, FDA, *CDER 21st Century Review Process: Desk Reference Guide* 37 (2014), https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf; see also FDA, *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products* 21 (Apr. 2005), https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079748.pdf (addressing "communication between the FDA and applicants" during "labeling discussions").

they will "make every reasonable effort to communicate [them] promptly to applicants." 21 C.F.R. 314.102(b). And if only "editorial or similar minor deficiencies in the [proposed] labeling" exist, FDA may approve the supplement on the condition that the applicant makes appropriate corrections and submits a copy of the final labeling before marketing the drug with that labeling. 21 C.F.R. 314.105(b).

FDA will reject a supplement, however, if the proposed labeling change is false or misleading or if it does "not comply with the requirements for labels and labeling in [21 C.F.R. P]art 201." 21 C.F.R. 314.125(b)(6) and (8). In such circumstances, FDA will send the applicant a "complete response letter." 21 C.F.R. 314.110(a). A complete response letter reflects FDA's "complete review of the data submitted" and "will describe all of the specific deficiencies that the agency has identified." 21 C.F.R. 314.110(a)(1) and (2).

2. a. Petitioner is the manufacturer of Fosamax, a brand-name drug that FDA approved in tablet form in 1995 for the treatment of osteoporosis in postmenopausal women. Pet. App. 5a, 12a; see p. 2 n.1, *supra*. Evidence later began to emerge suggesting a connection between Fosamax and an increased risk of an unusual type of thigh-bone fracture known as an "atypical femoral fracture[]," which occurs with no or minimal external trauma and results in a complete fracture of the femur. Pet. App. 6a, 13a-14a. Petitioner kept FDA informed of those studies. *Id.* at 13a.

In June 2008, FDA informed petitioner that it was aware of reports regarding the occurrence of fractures in patients using bisphosphonates like Fosamax. Pet. App. 14a. FDA stated that it was "concerned about this developing safety signal" and asked petitioner to submit

any information it had on the issue. *Ibid.* (citation omitted). Petitioner promptly complied. *Ibid.*

b. In September 2008, petitioner submitted three Prior Approval Supplements for its three Fosamax products that proposed changing the relevant labeling to address atypical femoral fractures in two respects. Pet. App. 14a-15a; see p. 2 n.1, *supra*.[6] First, in the Adverse Reactions section, petitioner proposed adding a reference to "low-energy femoral shaft fracture." Pet. App. 16a (quoting C.A. App. A1383). Second, in the Warnings and Precautions section, petitioner proposed adding a new subsection with an identical title: "Low-Energy Femoral Shaft Fracture." *Id.* at 15a (quoting C.A. App. A1371) (emphasis omitted). That subsection stated that "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients." C.A. App. A1371. The proposed warning added that "[s]ome" of those fractures were "stress fractures," and the remainder of petitioner's proposed text repeatedly referenced stress fractures. *Ibid.*

Petitioner supported its applications with evidence regarding femoral fractures in Fosamax users. Pet. App. 16a. The applications stated, *inter alia*, that petitioner's use of the term "stress fracture" in connection with reports of "low-energy subtrochanteric/mid femoral shaft fractures" referred to an "insufficiency fracture" that occurs with no "identifiable external traumatic event." C.A. App. A2751-A2752; see *id.* at

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[6] Relevant portions of one of the PAS applications are available at C.A. App. A2697-A2928. See *id.* at A1349-A1388 (duplicative). FDA has confirmed to this Office that petitioner proposed the same relevant labeling language for each of its three Fosamax products.

A2754.[7] The treatment data in the applications indicated that 91% of the fractures resulted in surgical intervention and the other 9% involved patients who sustained only "incomplete stress fractures." *Id.* at A2755.

In May 2009, FDA issued a Complete Response Letter informing petitioner that FDA could not "approve the[] applications in their present form." Pet. App. 18a (quoting C.A. App. A1500). FDA stated that it "agree[d] that atypical and subtrochanteric fractures should be added" to the Adverse Reactions labeling section. C.A. App. A1500. FDA therefore "recommend[ed]" that petitioner modify its proposed text for that section to read "low energy femoral shaft and subtrochanteric fractures." *Id.* at A1501. With respect to petitioner's Warnings and Precautions proposal, however, FDA determined that the "justification for the proposed [Warnings and Precautions] section language is inadequate." *Id.* at A1500. The letter also stated that "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature" and that "[d]iscussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting." *Id.* at A1500-A1501.

In June 2009, petitioner updated the Adverse Reactions section of its Fosamax labeling using FDA's recommended text. C.A. App. A1141, A1143. Petitioner

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[7] An "insufficiency f[racture]"—which can be associated with "osteoporosis"—is "a stress fracture that occurs during normal stress on a bone of abnormally decreased density"; it is thus different from the type of "stress f[racture]" experienced by athletes (a fatigue fracture) "caused by unusual or repeated stress on a bone." *Dorland's Illustrated Medical Dictionary* 710-711 (29th ed. 2000).

then withdrew its three pending PASs and submitted new CBE supplements for that labeling change (which FDA later approved) as the "quickest route to update" its labeling. 11-cv-5304 Doc. 26, Ex. 12, at 6279, 64,461.[8]

c. Nearly a year after its Complete Response Letter, and after reviewing additional data submitted by petitioner and other manufacturers, FDA issued a Safety Announcement in March 2010 stating that the data at that time had "not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures," but that FDA was working with an outside expert task force to gather additional information. C.A. App. A1508; see Pet. App. 19a.

In September 2010, the task force completed its report, which identified an apparent association between long-term bisphosphonate use and certain atypical femoral fractures. Pet. App. 20a. In October 2010, FDA announced that it was requiring bisphosphonate manufacturers to modify their labeling to include information regarding the risk of such fractures in, *inter alia*, the Warnings and Precautions section. C.A. App. A1118. Shortly thereafter, FDA approved that labeling change for Fosamax. Pet. App. 21a-23a. Before approving that labeling, FDA eliminated references to "stress fractures" from petitioner's proposal because, FDA concluded, the term would suggest to most practitioners "a minor fracture" that "would contradict the seriousness

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[8] See FDA, *Supplement Approval* 1-2 (Mar. 1, 2010), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/020560s051s055s057,021575s012s016s018ltr.pdf (NDA 20560/S-057 and 21575/S-018); FDA, *Supplement Approval* 1-2 (Mar. 1, 2010), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/021762s005s009sS010ltr.pdf (NDA 21762/S-010).

of the atypical femoral fractures" at issue. *Id.* at 22a-23a (citation omitted).

3. Over 1000 plaintiffs subsequently filed separate state-law tort actions against petitioner, alleging that they had sustained atypical femoral fractures caused by taking Fosamax. Pet. App. 4a, 23a. Although plaintiffs asserted an array of tort theories, they generally alleged that petitioner had failed to provide adequate warnings on its Fosamax labeling. *Id.* at 4a, 24a. The cases were consolidated for pretrial proceedings as a multidistrict litigation (MDL). *Id.* at 23a.

One bellwether case within the MDL was selected for trial on its failure-to-warn claim. Pet. App. 24a-25a & n.64. Petitioner moved for summary judgment on preemption grounds, but the district court did not immediately rule on the motion. *Id.* at 163a. After a jury rendered a verdict for petitioner on case-specific grounds, the court rendered a post-trial decision holding that the bellwether plaintiffs' failure-to-warn claim was preempted. *Id.* at 25a-26a, 153a-174a.

The district court subsequently applied that holding to the other MDL cases in which the plaintiff was injured before September 14, 2010—the date of the FDA task force report—and granted judgment to petitioner in those cases. Pet. App. 152a; see *id.* at 113a-152a.

4. The court of appeals vacated and remanded. Pet. App. 1a-74a.

The court of appeals concluded that its impossibility-preemption analysis was controlled by this Court's decision in *Wyeth* v. *Levine*, *supra*, which the court viewed as teaching that a drug-focused failure-to-warn claim is preempted "where there is 'clear evidence that the FDA would not have approved a change' to the label," Pet. App. 32a-33a (quoting *Wyeth*, 555 U.S. at 571). See *id.*

at 28a-55a. The court concluded that *Wyeth*'s "clear evidence" discussion "announce[d] a standard of proof" that is "synonymous with 'clear and convincing evidence'" and required proof showing it "is highly probable that the FDA would not have approved a change to the drug's label." *Id.* at 35a, 37a; see *id.* at 33a-37a. The court further concluded that the relevant preemption determination—which involves "predict[ing] how the FDA would have reacted in a hypothetical scenario" involving a new proposal to strengthen labeling warnings, *id.* at 51a-52a—is a factual determination for a jury, not a legal one for a court. *Id.* at 38a-55a.

Applying those principles, the court of appeals held that summary judgment should not have been granted to petitioner. Pet. App. 55a-74a. As relevant here, the court determined that a "reasonable jury" could conclude that petitioner could have revised the Warnings and Precautions section of its labeling before September 2010. *Id.* at 56a-57a, 67a. A jury, the court reasoned, could find that FDA's 2009 decision to reject petitioner's proposed revision to that section was not based on FDA's determination that the evidence at the time was insufficient to indicate that Fosamax caused atypical femoral fractures, but rather was based on FDA's dissatisfaction with the proposal's use of the term "stress fractures," which medical practitioners might misunderstand to refer to fractures less serious than the femoral fractures in question, *id.* at 64a-66a. See *id.* at 59a-68a.[9]

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[9] The court of appeals also concluded that the district court erred in granting summary judgment on claims based on the Adverse Reactions section of Foxamax's labeling before its 2009 revision, Pet. App. 69a-73a, and on non-failure-to-warn claims, *id.* at 74a.

DISCUSSION

The court of appeals erred in holding that a jury must determine whether FDA's May 2009 decision—which declined to approve petitioner's proposal to revise Fosamax's Warnings and Precautions section to warn against "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft," C.A. App. A2720—preempted respondents' state-law failure-to-warn claims arising from that same type of injury. Where, as here, FDA renders a decision declining to approve a drug-labeling change, the interpretation of that administrative decision and its significance for a failure-to-warn claim are legal questions for a court to resolve, not factual questions for a jury. Moreover, because FDA's decision here prevented petitioner from modifying the relevant labeling before late 2010, the court of appeals erred in rejecting petitioner's impossibility-preemption defense.

In the view of the United States, this Court should grant review. The underlying issue—whether the meaning and effect of an FDA labeling decision present a question of law for courts to resolve or a question of fact for lay juries to determine—is significant. The petition cleanly presents that issue in a context in which hundreds of separate cases asserting similar failure-to-warn claims turn on its proper resolution. No circuit conflict yet exists, however, and further percolation in the courts of appeals could potentially refine the issue for review. Although the question is close, the government concludes that, on balance, review is warranted at this time.

I. THE COURT OF APPEALS ERRED IN REJECTING PETITIONER'S PREEMPTION DEFENSE

A. The Meaning And Effect Of FDA's May 2009 Decision Present A Legal Question That A Court Must Resolve

The court of appeals held that the relevant task in resolving petitioner's preemption defense "is to predict how the FDA would have reacted in a hypothetical scenario" involving "a different label amendment than the one it actually rejected in [its] May 2009 letter." Pet. App. 51a-52a. The court thus concluded that the proper focus is not the "legal effect" of FDA's May 2009 decision but what the agency's decision letter "suggests about the FDA's likely response to a differently worded proposal." *Id.* at 52a. That is incorrect. The proper focus here is on whether FDA's May 2009 decision embodied a determination by FDA that insufficient causal evidence existed at the time to warrant strengthening Fosamax's Warnings and Precautions section to address atypical femoral fractures. That is a question of law for a court to resolve, not a question of fact for a jury.

1. A federal agency's written decision on a regulatory application is a legal document: an agency action that embodies the agency's exercise of legal authority to adjudicate that application. *Cf.* 5 U.S.C. 551(6) and (7) (defining agency adjudication). The meaning and effect of such agency action is a legal question within the exclusive province of a court.

When Congress enacted the Administrative Procedure Act (APA), 5 U.S.C. 551 *et seq.*, 701 *et seq.*, it specified that a "reviewing court shall * * * determine the meaning or applicability of the terms of an agency action." 5 U.S.C. 706. That provision reflects the longstanding view that the "application" of "any agency action" and "questions respecting the * * * terms of

[such] action" are "questions of law" and therefore matters for "courts * * * to decide." H.R. Rep. No. 1980, 79th Cong., 2d Sess. 44 (1946); see U.S. Dep't of Justice, *Attorney General's Manual on the Administrative Procedure Act* 108 (1947) (APA's review provision "restates the present law").

The legal nature of that inquiry is consistent with this Court's precedent addressing the meaning and effect of a prior judicial adjudication. When issues adjudicated in prior litigation are relevant to factfinding in a subsequent civil action, this Court has held that the question of "[w]hat issues were decided [in that prior] litigation is * * * a question of law" that the trial court must itself decide by examining relevant materials from the prior case. *Emich Motors Corp.* v. *General Motors Corp.*, 340 U.S. 558, 571-572 (1951). That holds true even where a jury must consider "the scope and effect of the former judgment on the case at trial"; in such circumstances, the trial court must first determine the prior adjudication's scope and effect before "instruct-[ing] the jury" on its legal determination. *Ibid.* Just as the scope of such a prior judicial adjudication is a question of law for a court to decide, so too is the scope of a federal agency adjudication like that at issue here.

No sound reason exists for treating the meaning and effect of an FDA administrative determination any differently. Judges, rather than lay juries, are best suited to evaluate the scope of an agency's legal determination in light of the relevant statutory and regulatory context. Moreover, framing the decision as a question of law to be decided by judges familiar with principles of administrative law will foster the type of uniformity appropriate when determining the scope and effect of federal agency action. See *Markman* v. *Westview Instruments,*

Inc., 517 U.S. 370, 390-391 (1996). Whether the agency action is a notice-and-comment regulation or something less formal like the adjudicatory decision at issue here, the meaning of such agency action is a legal question that a court should decide. Cf. *Perez* v. *Mortgage Bankers Ass'n*, 135 S. Ct. 1199, 1208 n.4 (2015) ("[I]t is the court that ultimately decides wh[at] a given regulation means.").

In this case, as explained below, the basis for FDA's 2009 Fosamax labeling decision is properly determined as a matter of law from FDA's Complete Response Letter, read in the context of petitioner's underlying labeling supplement and the surrounding regulatory framework and related FDA actions. Even if disputed subsidiary factual questions were relevant to determining the meaning and effect of the agency's 2009 decision, the ultimate inquiry would remain a legal one. This Court in *Markman* confronted analogous circumstances when it held that "the construction of a patent" is a "purely legal" issue "exclusively within the province of the court." 517 U.S. at 372, 391. The Court reasoned that "judges, not juries, are the better suited" for discerning the meaning of patent terms, even though factual questions involving "credibility determinations" are sometimes "subsumed" within the relevant analysis. *Id.* at 388-389; see *Teva Pharm. USA, Inc.* v. *Sandoz, Inc.*, 135 S. Ct. 831, 838 (2015) (explaining that the "ultimate issue of the proper construction of a [patent] claim [is] treated as a question of law," even though "subsidiary factfinding is sometimes necessary"). The same rationale applies here. To the extent extrinsic evidence may sometimes be relevant to determine the meaning and effect of FDA's agency action in litigation

between private parties (which typically will lack compilation of an official administrative record), the court's evaluation of such subsidiary facts does not alter the ultimate legal character of the inquiry.

2. The court of appeals concluded that, in order to sustain petitioner's preemption defense, this Court's decision in *Wyeth* v. *Levine*, 555 U.S. 555 (2009), required that petitioner provide "clear evidence" that could establish to a jury that FDA "would [have] reject[ed] [the] plaintiff's proposed warning" for Fosamax if petitioner had proposed that warning to FDA. Pet. App. 33a, 54a. In addressing that purported "hypothetical scenario," the court of appeals determined that a jury could reasonably conclude that "FDA rejected [petitioner's] proposed warning about femoral fractures in 2009 not because" FDA deemed the "causal link between Fosamax and fractures" to be insufficient, but because FDA was dissatisfied with petitioner's proposed text. *Id.* at 51a, 64a-65a. Nothing is "hypothetical" about FDA's *actual* 2009 decision in this case, and nothing in *Wyeth* addresses how courts should determine the meaning and effect of such (actual) agency action.

In *Wyeth*, this Court determined that a state-law failure-to-warn claim involving a brand-name drug was not foreclosed by the doctrine of impossibility preemption, because the drug manufacturer had a duty to ensure the adequacy of its own labeling and could have invoked FDA's CBE regulation to update its labeling promptly to provide additional warnings in response to newly acquired information. 555 U.S. at 570-573. The Court recognized that "FDA retains authority to reject [a manufacturer's unilateral] labeling changes made pursuant to the CBE regulation," *id.* at 571, but it explained that Wyeth did "not argue" that any actual FDA

decision had "prohibited" it from strengthening its labeling, *id.* at 572.

The Court instead viewed Wyeth as arguing that FDA had "intended to prohibit it" from changing the label when FDA originally approved the relevant drug, a contention that the courts below had rejected. 555 U.S. at 572 & n.5. Thus, without any actual agency decision at hand, this Court stated that it would not conclude that it was impossible for Wyeth to comply with both federal and state requirements "absent clear evidence that the FDA *would not have approved* a change to [the] label[ing]" in question. *Id.* at 571 (emphasis added). In other words, the Court reasoned that Wyeth needed to make a clear showing that "FDA would have rescinded any change in the label" to establish that it would have been impossible to make such a change. *PLIVA, Inc.* v. *Mensing*, 564 U.S. 604, 624 n.8 (2011). This Court then rejected Wyeth's impossibility defense because the manufacturer, which did "not argue" that it had provided FDA with an analysis of the "specific dangers" in question, failed to show that "FDA would have prevented it from adding a stronger warning." 555 U.S. at 572-573.

Because *Wyeth* discussed the question whether FDA would have rejected a CBE labeling change *if* the manufacturer in that case had unilaterally made such a change to strengthen its labeling, *Wyeth* did not resolve how to determine the meaning and effect of an actual FDA labeling-supplement decision. For that reason, the court of appeals erred in transplanting *Wyeth*'s discussion about a hypothetical regulatory scenario to support a requirement for "clear evidence" about the scope and effect of the actual agency labeling decision in this

case. This Court has long cautioned that it is "often misleading" to transplant "[g]eneral expressions" from one opinion "to other facts" because every opinion must be "read in the light of the facts of the case under discussion." *Armour & Co.* v. *Wantock*, 323 U.S. 126, 133 (1944); see *Landgraf* v. *USI Film Prods.*, 511 U.S. 244, 265 (1994) (quoting *Cohens* v. *Virginia*, 19 U.S. (6 Wheat.) 264, 399 (1821) (Marshall, C.J.)).

3. This case does not present circumstances in which there is no actual FDA labeling decision to interpret—for instance, because the manufacturer did not submit a labeling supplement. In such circumstances, *Wyeth*'s use of the phrase "clear evidence" could arguably be read to suggest that determining what FDA would have done with respect to such a supplement presents a question of fact for the jury to decide. See Pet. App. 33a-55a. But *Wyeth* did not squarely address or definitively resolve that issue with the phrase "clear evidence." See *id.* at 28a, 33a-35a (noting that *Wyeth*'s discussion was "cryptic"). This Court in another context, for example, has used the even more specific phrase "clear and convincing evidence" not in its "strict evidentiary sense" but merely as a "useful reminder" that a general presumption concerning a *legal interpretation* should control if substantial doubt exists about "congressional intent." *Block* v. *Community Nutrition Inst.*, 467 U.S. 340, 350-351 (1984). By analogy here, *Wyeth* may simply reflect that a persuasive legal showing is necessary to establish preemption when no relevant FDA decision exists.

Wyeth therefore may be understood as consistent with the view that, to establish impossibility preemption, a name-brand drug manufacturer cannot rely on

speculation or merely plausible interpretations of ambiguous features of FDA's regulatory framework and practices. Rather, on this understanding of *Wyeth*, the manufacturer must demonstrate, on the basis of historical facts concerning its own conduct and available studies and data at the time, that the agency reasonably would have concluded that a labeling change was not warranted under the relevant statutory and regulatory framework. This case does not require the Court to consider that scenario, however, because the relevant question here is how to interpret FDA's actual labeling decision in this case.

B. FDA's May 2009 Decision Rejected A Change To Fosamax's Warnings And Precautions Because The Data At That Time Was Insufficient To Justify A Change

FDA's May 2009 decision rejecting petitioner's proposal to modify Fosamax's Warnings and Precautions section to address atypical femoral fractures was based on the agency's determination that the data was then insufficient to justify such a warning. That conclusion flows directly from the terms of the agency's May 2009 Complete Response Letter, the relevant regulatory context, and the agency's subsequent actions. Given FDA's determination, respondents' claim that petitioner should have updated its Warnings and Precautions labeling at that time is preempted.[10]

FDA's Complete Response Letter (C.A. App. A1500-A1501) shows that FDA determined that the existing data for atypical femoral fractures was sufficient to update Fosamax's Adverse Reactions section, but not its

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[10] The question presented is based on the premise that petitioner provided FDA with "the relevant scientific data," Pet. i, and respondents' brief in opposition does not appear to contend otherwise.

Warnings and Precautions section. FDA determined that "atypical and subtrochanteric fractures should be added" as adverse reactions, *id.* at A1500, reflecting that FDA found "some basis to believe there [wa]s a causal relationship between the drug and the occurrence of th[at] adverse event." 21 C.F.R. 201.57(c)(7). Petitioner's proposed Warnings and Precautions revision was based on the same risk. Among other things, petitioner's proposed title ("Low-Energy Femoral Shaft Fracture") for its proposed subsection in Warnings and Precautions was identical (with only differing capitalization) to its proposed text for the Adverse Reactions section. Pet. App. 15a-16a (citation and emphasis omitted). The proposed warning also addressed the same type of adverse reaction that FDA agreed should be added to Fosamax's labeling. See *id.* at 15a ("[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft") (citation omitted).

Under the governing regulations, however, such an adverse reaction is to be elevated to the Warnings and Precautions section only if "reasonable evidence of a causal association with [the] drug" exists. 21 C.F.R. 201.57(c)(6)(i). Here, FDA rejected petitioner's addition because the "*justification* for the proposed [Warnings and Precautions] section language [wa]s inadequate." C.A. App. A1500 (emphasis added). Petitioner had also proposed stating that "[s]ome" of the reported fractures were "insufficiency" "stress fractures," *id.* at A1371; see pp. 7-8 & n.7, *supra*, but FDA determined that such fractures "may not be clearly related to the atypical subtrochanteric fractures * * * *reported in the literature*," and the associated discussion of stress-fracture risk factors was likewise "not adequately *supported by the available literature and post-marketing*

adverse event reporting." C.A. App. A1500-A1501 (emphases added). FDA's decision thus was based on the lack of adequate data to support a warning.

The court of appeals focused instead on the possibility that "FDA [might have] rejected [petitioner's] proposed warning" because of the warning's use of the term "stress fractures." Pet. App. 64a-65a. But a Complete Response Letter reflects "FDA's complete review of the *data* submitted"; the letter need not address any "proposed product labeling" if FDA determines that the "data submitted are inadequate." 21 C.F.R 314.110(a)(2) and (3) (emphasis added). If a warning is warranted, FDA will attempt promptly to identify easily correctable deficiencies in the proposed text and will then develop final labeling text with the manufacturer in an iterative process. See pp. 5-6, *supra*. The May 2009 letter thus embodies FDA's "recommend[ation]" that petitioner modify its proposed Adverse Reactions text with language (shown here in italics) that FDA itself proposed: "low energy femoral shaft *and subtrochanteric* fractures." C.A. App. A1501 (emphasis added); cf. Pet. App. 16a (petitioner's proposal). And in late 2010, when FDA concluded that the Warnings and Precautions section should also be revised, FDA itself edited petitioner's language to remove stress-fracture references it deemed insufficiently clear. Pet. App. 22a-23a. No sound basis thus exists for concluding that FDA determined in May 2009 that the data was sufficient to warrant a warning but that it rejected petitioner's proposal because of petitioner's proposed text.

FDA's own regulations require that the Warnings and Precautions section "must be revised" to add such a clinically significant hazard "*as soon as*" sufficient

causal evidence exists. 21 C.F.R. 201.57(c)(6)(i) (emphasis added). If FDA had "believe[d]" in May 2009 that the "new safety information" that petitioner had submitted "should [have] be[en] included in [Fosamax's] labeling," Section 355(*o*)(4) would have required that FDA "promptly notify" petitioner, 21 U.S.C. 355(*o*)(4)(A), and engage in expedited discussions to revise the labeling, 21 U.S.C. 355(*o*)(4)(B)-(D). In 2009, however, FDA concluded in its Complete Response Letter that the justification for an enhanced warning was insufficient. Indeed, nearly a year later, FDA announced—after reviewing further data—that it had yet to find any "clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures." Pet. App. 19a (citation omitted). It was only in October 2010—after an external task force had completed its report on the issue—that FDA came to "believe that the information" about atypical femoral fractures should be added to the Warnings and Precautions section and therefore invoked Section 355(*o*)(4) to revise the labeling for Fosamax and other bisphosphonates. See C.A. App. A1515-A1516.

II. THE COURT OF APPEALS' DECISION WARRANTS REVIEW

Although the question is close, in the view of the United States, this Court should grant certiorari. The underlying issue in this preemption case is a significant one: whether the meaning and effect of an FDA labeling decision is a question of law for courts to resolve or a question of fact for lay juries to determine. The petition cleanly presents that issue in an MDL context in which hundreds of separate cases asserting similar failure-to-

warn claims turn on its proper resolution. The hundreds of trials that could ensue are unlikely to clarify the issue for review.

To be sure, petitioner correctly does not contend that the court of appeals' decision here has yet given rise to a circuit conflict. Cf. Pet. 14. It is also unclear whether the decision below will influence other courts addressing similar preemption defenses. No court of appeals, for instance, has focused on the principle that the interpretation of federal agency action is traditionally a legal question for courts to decide. Allowing the issue to "mature through full consideration by the courts of appeals" could thus potentially "simplif[y the Court's] task" by refining the issue for its review. *E.I. du Pont de Nemours & Co.* v. *Train*, 430 U.S. 112, 135 n.26 (1977).

On balance, however, the government concludes that review is warranted at this time. The legal question, although narrow in the context of this case involving an FDA decision rejecting a proposed labeling change, is important and cleanly presented. Its practical implications are starkly illustrated by the volume of tort claims asserted against petitioner in this case. And the Court's consideration of the proper method for resolving the preemption issue in this case may inform the proper analytical framework for resolving FDA preemption issues in light of *Wyeth* more generally.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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RECORD AND BRIEF

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IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,

Petitioner,

v.

DORIS ALBRECHT, ET AL.,

Respondents.

On Petition For a Writ of Certiorari
To the United States Court of Appeals
For the Third Circuit

BRIEF OF AMICUS CURIAE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA IN SUPPORT OF PETITIONER

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INTEREST OF AMICUS CURIAE

The Pharmaceutical Research and Manufacturers of America (PhRMA) is a voluntary nonprofit association representing the country's leading research-based pharmaceutical and biotechnology companies.[1] PhRMA advocates in support of public policies that encourage the discovery of life-saving and life-enhancing new medicines. PhRMA members produce innovative medicines, treatments, and vaccines that save and improve the lives of countless individuals every day. PhRMA members have invested more than half a trillion dollars in R&D since 2000, and in 2016 alone invested $65.5 billion in discovering and developing new medicines. PhRMA, *Biopharmaceuticals in Perspective: Spring 2017*, at 35 (2017), http://phrma-docs.phrma.org/files/dmfile/Biopharmaceuticals-in-Perspective-2017.pdf [hereinafter *Biopharmaceuticals in Perspective*].

This case presents a question of critical importance for PhRMA's members: whether, after the Food and Drug Administration (FDA) rejects a company's proposed warning for a medicine, the company may nonetheless be held liable under state law for failing to provide the warning the FDA rejected. This question has arisen repeatedly in lawsuits brought

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[1] Pursuant to Rule 37.6, *amicus* affirms that no counsel for a party authored this brief in whole or in part and that no person other than *amicus*, its members, or its counsel made any monetary contributions intended to fund the preparation or submission of this brief. A list of PhRMA members is available at http://www.phrma.org/about/members. Merck & Co. is a member of PhRMA, but did not contribute financially to the preparation of this brief. The parties were timely notified of *amicus*'s intent to file this brief and consented to its filing.

against PhRMA's members and has perplexed the lower courts. The Court should grant the Petition and establish clear, consistent, and fair preemption rules for FDA-rejected warnings.

INTRODUCTION AND SUMMARY OF ARGUMENT

The FDA brings extensive scientific expertise to bear in approving medically-appropriate labeling for prescription medicines both before and after they are brought to market. Congress granted the FDA this authority in recognition of its unique institutional ability to evaluate the scientific basis for proposed warnings and assess how best to communicate complex risk and benefit information about medicines. In recognition of that authority, this Court held in *Wyeth v. Levine*, 555 U.S. 555 (2009), that state-law tort claims are preempted when the FDA would have rejected the labeling that a plaintiff asserts was required by state law.

The Third Circuit's decision undermines the FDA's authority to control the content of medicine labeling and at the same time places manufacturers in the impossible position of facing civil liability for not adopting warnings that the FDA prohibited them from adopting. In this case, after considering the available scientific evidence, the FDA rejected Merck's proposal to include a warning for the precise risk Plaintiffs subsequently claimed should have been included in the label. The FDA's decision was not based on some narrow objection to the specific language of Merck's proposal. To the contrary, the FDA's rejection was accompanied by no counter-proposal, notwithstanding the agency's statutory obligation to

work collaboratively with manufacturers to develop warnings for safety issues that the agency believes should be reflected in labeling.

Yet the Third Circuit reversed the district court's determination that these facts warrant preemption of Plaintiffs' state-law claims, holding that preemption is a factual determination reserved for jury resolution absent a "'smoking gun' rejection letter" laying out the FDA's rationale for rejecting the warnings sought. Pet. App. 55. That standard is untenable. The Third Circuit's unrealistic preemption standard will expose manufacturers to immense liability that will hamper innovation and endanger public health. In addition, the Third Circuit's standard will incentivize manufacturers to inundate the FDA with linguistic variants of labeling requests in the hope that multiple rejections will be sufficient to trigger preemption.

As numerous courts have indicated, and as the decision below reflects, lower courts have struggled to apply Levine's "clear evidence" standard. The Court should grant the Petition to provide much-needed guidance.

ARGUMENT

I. The Court Should Address An Important and Recurring Issue that Lower Courts Have Struggled to Resolve

In *Levine*, the Court held that Wyeth had presented no "clear evidence" that the FDA would not have approved a change to Phenergan's label. 555 U.S. at 571. In that case, moreover, the Court emphasized that FDA had never given "more than passing

attention" to the instruction plaintiffs sought. *Id.* at 572. Lacking guidance from this Court about the type and quantum of evidence that suffices to demonstrate the FDA "intended to prohibit [the manufacturer] from strengthening the warning," *Levine*, 555 U.S. at 572, lower courts have struggled to faithfully apply *Levine*'s holding. *See, e.g.*, Pet. App. 29 ("This [clear evidence] standard is cryptic and open-ended, and lower courts have struggled to make it readily administrable."); *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 391 (7th Cir. 2010) ("The Supreme Court . . . did not clarify what constitutes 'clear evidence.' Therefore, the only thing we know for sure is that the evidence presented in *Levine* did not meet this exacting standard.").

That difficulty is confirmed by inconsistencies in *Levine*'s application. *Compare, e.g.*, *Mason*, 596 F.3d at 396 (finding the record did not show "clear evidence" FDA would have rejected an enhanced suicidality warning for an SSRI), *with Dobbs v. Wyeth Pharm.*, 797 F. Supp. 2d 1264, 1277-80 (W.D. Okla. 2011) (finding "clear evidence" FDA would have rejected an enhanced suicidality warning for an SSRI and distinguishing SSRI cases with different outcomes); *also compare Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861 (7th Cir. 2010) (finding "clear evidence" the FDA would have rejected a children's Motrin label warning for SJS/TEN where FDA did not require mention of SJS/TEN on the label), *with Reckis v. Johnson & Johnson*, 471 Mass. 272 (2015), *cert. denied*, 136 S. Ct. 896 (2016) (finding the record did not show "clear evidence" under facts similar to *Robinson*).

In the eight years since this Court decided *Levine*, the issue of preemption and the meaning of "clear evidence" has arisen in over 100 decisions available on Westlaw from trial and appellate courts around the country, and the issue of preemption figures prominently in every one of the tens of thousands of pharmaceutical product liability lawsuits nationwide. Absent further guidance, lower courts will continue to struggle with *Levine*'s application. This case presents an excellent opportunity for the Court to refine *Levine*'s "clear evidence" standard in the context of a detailed regulatory record.

II. The Third Circuit's Decision Disregards the Realities of FDA Labeling Review, Thereby Threatening Its Effectiveness

The Third Circuit's decision gives insufficient deference to the FDA's extensive labeling oversight. It also creates conditions under which the FDA's review capabilities will be strained, thus weakening FDA's ability to protect public health.

A. The Comprehensive FDA Regulatory Regime Ensures that Labeling Contains a Summary of the Essential, Scientifically-Grounded Safety Information

Effective pharmaceutical labeling strikes a delicate balance. Labeling must convey a wealth of information necessary for the safe and effective use of a medicine. At the same time, this information must be communicated in a manner that is useful to healthcare professionals. One way in which labeling

achieves this balance is by providing information only when it is scientifically-based.

Striking this balance is critically important because patients may be harmed when labeling communicates unfounded safety information. First, physicians may disregard lengthy labeling weighted down with speculative warnings, thereby overlooking important, scientifically-founded safety information. *See, e.g.*, *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 869 (7th Cir. 2010) ("The resulting information overload [from describing every remote risk] would make label warnings worthless to consumers."); *Thomas v. Hoffman-LaRoche, Inc.*, 949 F.2d 806, 816 n.40 (5th Cir. 1992) (explaining that if manufacturers were required to clutter their warnings with "every possible risk," then "physicians [would] begin to ignore or discount the warnings"); FDA, Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49,603, 49,605–06 (Aug. 22, 2008) (final rule) (unfounded statements in FDA labeling may cause "more important warnings" to be "overshadow[ed]").

Second, warnings that are not grounded in science discourage the beneficial use of medicines. *See, e.g.*, *Mason*, 596 F.3d at 392 (7th Cir. 2010) ("[O]verwarning can deter potentially beneficial uses of the drug by making it seem riskier than warranted . . . ."); *Dowhal v. SmithKline Beecham Consumer Healthcare*, 88 P.3d 1, 14 (Cal. 2004) ("[A] truthful warning of an uncertain or remote danger may mislead the consumer into misjudging the dangers stemming from use of the product, and consequently

making a medically unwise decision."); 73 Fed. Reg. at 49,605–06 ("[O]verwarning . . . may deter appropriate use of medical products . . . ."). All medicines have risks, and all prescribing decisions are based on balancing those risks against the medicine's potential benefits. Distorting the true nature of that balance, by overstating unfounded or speculative risks, fundamentally inhibits medical professionals from making the most appropriate and medically-optimal prescribing decisions.

In order to ensure that "the public get[s] the accurate, science-based information they need," the FDA tightly regulates the labeling for all prescription medicines. *Statement of FDA Mission*, FDA, http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/budgetreports/ucm298331.pdf. FDA regulations provide detailed labeling requirements, dictating required categories, precise information each category should include, and, in many cases, exact formatting standards. *See* 21 C.F.R. §§ 201.56-57, 201.66, 201.80. As relevant here, medicine labeling must warn about any serious hazard for which there is "reasonable evidence of a causal association." 21 C.F.R. § 201.57(c)(6).

The FDA must approve labeling before a medicine can be marketed, and it continues to scrutinize labeling thereafter. Before a manufacturer can amend its labeling, it generally must obtain the FDA's approval through the submission of a "prior approval supplement" ("PAS") to its New Drug Application. *See* 21 C.F.R. § 314.70(b)(2)(v). Manufacturers can, in some circumstances, add or strengthen a warning to reflect "newly acquired information." *See id.*

§ 314.70(c)(6)(iii). Even then, however, a manufacturer cannot distribute the new labeling until it submits a "changes being effected" ("CBE") supplement to the FDA. *See id.* § 314.70(c)(3)–(6). Unless the FDA finds that "the evidence of a causal association satisfies the standard for inclusion in the labeling," *id.* § 314.70(c)(6)(iii)(A), it must retroactively reject the change and require the manufacturer to stop distributing products with the new labeling, *see id.* § 314.70(c)(6)–(7); 73 Fed. Reg. at 49,603 ("[A] CBE supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug . . . .").

In addition to reviewing changes that manufacturers propose, the FDA independently considers whether labeling remains adequate in light of FDA's continuous monitoring of adverse event reports and other research.[2] Once it "becomes aware of new safety information" that it "believes should be included in the labeling," the FDA must notify the manufacturer, which must either propose a change or explain why no change is warranted. *See* 21 U.S.C. § 355(o)(4)(A).[3] If

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[2] Manufacturers are required to report "serious and unexpected" adverse events to the FDA within 15 days of receipt and to periodically report all other adverse events. 21 C.F.R. § 314.80. The FDA also receives adverse event reports through a voluntary reporting system, MedWatch. *MedWatch: The FDA Safety Information and Adverse Event Reporting Program*, FDA, https://www.fda.gov/Safety/MedWatch/default.htm.

[3] Section 355(o)(4) was passed as part of the Food and Drug Administration Amendments Act of 2007 ("FDAAA"), Pub. L. No.

the FDA disagrees with the manufacturer's response, it is required to "initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes." *Id.* § 355(o)(4)(C).

In short, the FDA brings to bear on all pharmaceutical labeling its expert judgment about whether a risk should appear in a medicine's label and, if so, how best to convey that information, all without diluting the labeling with warnings unfounded by the scientific record.

B. The Third Circuit's Preemption Rule Incentivizes Manufacturers to Overwhelm the FDA's Review Capabilities

As interpreted by the Third Circuit, "clear evidence" requires a "'smoking gun' rejection letter." Pet. App. 55. That requirement mistakes the nature of FDA review by assuming that review is limited to the precise verbiage submitted. Under the FDAAA, the

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110–85, 121 Stat. 823. Even before the FDAAA expressly delegated this responsibility, the FDA possessed considerable practical ability to generate labeling changes through its ability to (1) withdraw approval of a medicine whose labeling was "false or misleading in any particular," 21 U.S.C. § 355(e), and (2) bring an enforcement action against the manufacturer for misbranding, *see id.* § 352(a). The FDAAA was passed after the occurrence of the events in *Levine*, and thus the Court did not have occasion to consider the import of the FDAAA on the preemption analysis. *See Levine*, 555 U.S. at 567 ("In 2007, *after Levine's injury and lawsuit*, Congress again amended the FDCA." (emphasis added)).

FDA cannot let linguistic disagreements stand in the way of medically-warranted warnings. If the FDA believes that a new risk should be included in a medicine's labeling, but "disagrees with the [manufacturer's] proposed changes," it "shall initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information, *and if so, the contents of such labeling changes*." 21 U.S.C. § 355(o)(4)(C) (emphasis added).

The FDA's outright rejection of Merck's labeling supplement without initiating a discussion about any particular wording provides dispositive confirmation that FDA did not believe any additional warning was appropriate at that juncture. Otherwise, the FDA would have been in direct violation of its statutory obligations. No rational preemption framework should presume such a dereliction of agency duty. Nor does it make sense to apply such a backwards presumption unless the agency has written a comprehensive "smoking gun" exposition of all the reasons why no change was scientifically warranted. But that is precisely the result reached by the Third Circuit. *Levine* does not impose such an upside-down outcome.

In this case, the evidence is clear that the FDA would have rejected *any* warning for atypical femoral fractures in 2009. After reviewing the evidence Merck submitted in support of its labeling change, the FDA instructed Merck to "hold off" on adding a warning while a task force considered whether any warning was "warranted." Pet. App. 17–18. Only after receiving the task force's recommendation did the FDA

conclude that atypical femoral fractures were "'potentially more closely related to'" Fosamax use than it had previously appreciated. Pet. App. 21.

The Third Circuit's contrary holding will also have the effect of impairing the FDA's ability to carry out its mission. In *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), this Court held that state law "fraud-on-the-FDA" claims are preempted, reasoning that such claims incentivize manufacturers "to submit a deluge of information that the [FDA] neither wants nor needs" out of "fear that their disclosures . . . will later be judged insufficient in state court," thereby creating "additional burdens on the FDA[]." *Id.* at 351. The Third Circuit's preemption standard creates the same incentives that *Buckman* found impermissible.

As this case demonstrates, the FDA rarely takes the time to memorialize the full scientific rationale for its labeling decisions, especially in the post-approval setting where it is constantly assessing a developing scientific record. Powerless to generate the evidence the Third Circuit's ruling demands through their own actions, manufacturers will have an incentive to seek other ways to generate proof that the FDA believed a warning to be scientifically unfounded. For instance, pharmaceutical manufacturers may submit variations of the same warning, as the FDA's rejection of multiple iterations of a warning provides strong evidence that the FDA's rejection stemmed from a disagreement over the necessity of a warning rather than the specific language proposed.

Diverting the attention of the FDA toward litigation-defensive submissions would place an

excessive burden on the agency, and so would be an exercise fraught with peril. *See* 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006) ("FDA reviews all [CBE] submissions . . . ."); *Lofton v. McNeil Consumer & Specialty Pharm.*, 672 F.3d 372, 380 (5th Cir. 2012) (when manufacturers are compelled "to flood the FDA with information" to protect against liability, the FDA "loses control over its ability, based on scientific expertise, to prescribe — and intelligently limit — the scope of disclosures necessary for its work"); Br. for the United States as Amicus Curiae Supporting Pet'r at 25, *Levine*, 555 U.S. 555 (2009) (No. 06-1249) ("[The FDA] could not reasonably be expected to *expressly* reject every possible variant of approved labeling as part of its decisional process. Indeed, it would underestimate the post hoc imagination of lawyers to think such an exhaustion of potential variants by the manufacturer or the agency is even possible."). *Levine* could not have intended such an illogical result.

III. The Third Circuit's Decision Will Disincentivize Innovation and Harm Public Health

Bringing a new medicine to market is a lengthy and expensive process. Before studying a new medicine in humans, a pharmaceutical company must conduct a broad range of laboratory and animal studies to test how the medicine works and assess its safety. 21 C.F.R. § 312.23(a)(8). If the results are promising, the company submits an Investigational New Drug application ("IND") to the FDA, outlining the preclinical study results and offering a plan for clinical trials in humans. 21 U.S.C. § 355(i)(2); 21 C.F.R. § 312.20(a)–(b). Only upon FDA approval of

the IND can a company begin to study the prospective medicine in humans. Those human clinical trials generally occur in three phases, each of which typically must be completed before the potential new medicine may undergo FDA review and approval. 21 C.F.R. § 312.21. On average, the clinical trial phase alone takes six to seven years to complete. PhRMA, *Modernizing Drug Discovery, Development and Approval* 1 (2016), http://phrmadocs.phrma.org/sites/default/ files/pdf/proactive-policy-drug-discovery.pdf. If clinical trial results show that the medicine's benefits outweigh its risks, the sponsoring company can seek the FDA's approval to market the medicine by submitting a New Drug Application ("NDA"). 21 U.S.C. § 355(b)(1). The NDA, which must contain, among other things, the results of the clinical and preclinical testing, proposals for manufacturing, and proposed labeling for the new medicine, *id.*, often exceeds 100,000 pages in length, PhRMA, *Biopharmaceutical Research & Development: The Process Behind New Medicines* 14 (2015), http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf.

Innovative companies undertake this process at tremendous expense. On average, developing and obtaining FDA approval of a new medicine takes ten to fifteen years and costs $2.6 billion. *Biopharmaceuticals in Perspective, supra,* at 29; *see also* Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health

Econ. 20 (2016).[4] PhRMA's member companies invest approximately one quarter of their total annual domestic sales on research and development — an estimated $65.6 billion in 2016. *Biopharmaceuticals in Perspective*, *supra*, at 35.

These research efforts also involve tremendous risk, as most compounds invented never attain FDA approval. Just one out of every 5,000 to 10,000 compounds under development, and just one out of every eight medicines entering clinical trials, obtains FDA approval. Press Release, PhRMA, PhRMA Statement Regarding Benefits of New Medicines (Apr. 30, 2013), http://www.phrma.org/press-release/phrma-statement-regarding-benefits-of-new-medicines; *Biopharmaceuticals in Perspective*, *supra*, at 29; *see also, e.g.*, Jared S. Hopkins & Michelle Cortez, *Lilly's Alzheimer's Disease Drug Fails in Final-Stage Trial*, Bloomberg (Nov. 23, 2016, 6:52 AM), https://www.bloomberg.com/news/articles/2016-11-23/lilly-s-alzheimer-s-disease-drug-fails-in-final-

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[4] These estimates understate the cost of approval, as the FDA frequently conditions approval on a requirement that a sponsor undertake additional clinical studies after approval. *See* 21 U.S.C. § 355(o)(3)(A). According to one estimate, more than three quarters of all new medicine approvals are accompanied by a commitment from the sponsor to conduct one or more post-marketing, or "Phase IV," studies. Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 Food & Drug L.J. 295, 300 (2006). PhRMA's member companies spend more than $8.8 billion annually conducting these studies. PhRMA, *Annual Membership Survey* 6 tbl.4 (2016), http://phrma-docs.phrma.org/sites/default/files/pdf/annual-membership-survey-results.pdf.

stage-trial (discussing an innovator's $3 billion investment in an Alzheimer's treatment medication that failed at the final stage of clinical testing).

Given the enormous costs associated with researching and developing a new medicine, the scope of litigation risk bears heavily on a company's decision to invest in innovation. *See* W. Kip Viscusi et al., *A Statistical Profile of Pharmaceutical Industry Liability, 1976-1989*, 24 Seton Hall L. Rev. 1418, 1419 (1994) ("[T]he net effect of the surge in liability costs ha[s] been to discourage innovation in the pharmaceutical industry."); Richard A. Epstein, *Legal Liability for Medical Innovation*, 8 Cardozo L. Rev. 1139, 1153 (1987) ("If in the aggregate the net gains are wiped out by the liability costs, then the product will no longer be made."). The scope of litigation against pharmaceutical companies is already immense and rapidly expanding. Last year, 21,517 product liability lawsuits were filed against pharmaceutical companies in federal courts alone, up from 6,791 lawsuits just five years ago and just 2,700 lawsuits in 2001.[5] Today, out of seventy-three pending product liability multidistrict litigation proceedings, twenty-eight involve pharmaceuticals.[6] By comparison, between 1960 and

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[5] *See* Admin. Office of the U.S. Courts, Table C-2A: *U.S. District Courts--Civil Cases Commenced, by Nature of Suit, During the 12-Month Periods Ending September 30, 2012 Through 2016*, http://www.uscourts.gov/sites/default/files/data_tables/jb_c2a_0930.2016.pdf; Lisa Girion, *State Vioxx Trial Is Set as Drug Suits Boom*, L.A. Times, June 27, 2006, at C1.

[6] *See* U.S. Judicial Panel on Multidistrict Litig., MDL Statistics Report - Distribution of Pending MDL Dockets by District (Aug.

1999, there were only five MDL product liability actions involving FDA-approved medicines.[7]

The anti-nausea drug Bendectin, used to treat severe morning sickness in pregnant women, illustrates how unpredictable and unfounded litigation risks heavily influence a company's decision to invest in innovation. After Bendectin was named as the cause of birth defects in thousands of lawsuits, its manufacturer withdrew the medicine from the market in 1983, only later to be vindicated by scientific studies showing that Bendectin posed no maternal fetal risk.[8] In 2013, after nearly thirty years off the market, Bendectin returned under a new name.[9] In the interim, however, hospital admissions for excessive vomiting during pregnancy had doubled, costing the

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15, 2017), http://www.jpml.uscourts.gov/sites/jpml/files/Pending_MDL_Dockets_By_District-August-15-2017.pdf.

[7] *See* Deborah R. Hensler, *Has the Fat Lady Sung? The Future of Mass Toxic Torts*, 26 Rev. Litig. 883, 897–902 tbl.1 (2007).

[8] *See* Joseph Sanders, *From Science to Evidence: The Testimony on Causation in the Bendectin Cases*, 46 Stan. L. Rev. 1, 7 (1993); Robert Brent, *Medical, Social, and Legal Implications of Treating Nausea and Vomiting of Pregnancy*, 186 Am. J. Obstetrics & Gynecology S262, S262–63 (2002); *see also* David E. Bernstein, *The Breast Implant Fiasco*, 87 Cal. L. Rev. 457, 460 (1999); Lars Noah, *Triage in the Nation's Medicine Cabinet: The Puzzling Scarcity of Vaccines and Other Drugs*, 54 S.C. L. Rev. 371, 392 (2002).

[9] *See* News Release, Food & Drug Admin., *FDA Approves Diclegis for Pregnant Women Experiencing Nausea and Vomiting* (Apr. 8, 2013).

U.S. economy $1.7 billion annually in time lost from work, caregiver time, and hospital expenses.[10]

The development of medicines for high-risk and vulnerable populations is especially susceptible to this phenomenon. It is thus no surprise that by 1990, eight of the nine major U.S. pharmaceutical companies that had been involved in researching and developing new contraceptives had abandoned their efforts.[11] According to a contemporaneous report from the National Research Council and the Institute of Medicine, "recent products liability litigation and the impact of that litigation on the cost and availability of liability insurance have contributed significantly to the climate of disincentives for the development of contraceptive products." *Id.* at 141. In 1989, the inventor of the birth control pill, Carl Djerassi, recommended changes to the product liability regime, commenting that "the United States is the only country other than Iran in which the birth-control clock has been set backward during the past decade."[12] The

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[10] *See* Nina Nuangchamnong & Jennifer Niebyl, *Doxylamine Succinate–Pyridoxine Hydrochloride (Diclegis) for the Management of Nausea and Vomiting in Pregnancy: An Overview*, 6 Int'l J. Women's Health 401, 401–02 (2014), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3990370/pdf/ijwh-6-401.pdf.

[11] Nat'l Research Council, Comm. on Contraceptive Dev., & Inst. of Med., Div. of Int'l Health, *Developing New Contraceptives: Obstacles and Opportunities* 59 (Luidi Mastroianni et al. eds., 1990), https:// www.nap.edu/read/1450.

[12] Carl Djerassi, *The Future of Birth Control*, Wash. Post (Sept. 10, 1989), https://www.washingtonpost.com/archive/opinions/1989/09/10/the-future-of-birth-control/7e25f2cc-ae35-4a79-8daf31db02f81be/31db02f81be/?utm_term=.dd4d8bbcf626.

executive director of the Society for the Advancement of Women's Health Research similarly testified before Congress that "the current liability climate is preventing women from receiving the full benefits that science and medicine can provide." S. Rep. No. 104-69, at 7 (1995).

To be sure, the Court in *Levine* accepted the notion that diminished incentives for research and production of medicines might be offset by the possibility of uncovering "unknown drug hazards" and "incentives for drug manufacturers to disclose safety risks promptly." 555 U.S. at 579. But where the manufacturer promptly brings the potential safety risks to the FDA and the agency disagrees about the necessity of a warning, subsequent civil litigation serves no such purpose and works only to undermine the FDA's supremacy over the labeling process under the FDAAA. *See Levine*, 555 U.S. at 582 ("But it is also possible that state tort law will sometimes interfere with the FDA's desire to create a drug label containing a specific set of cautions and instructions.") (Breyer, J., concurring); *see also Riegel v. Medtronic, Inc.*, 552 U.S. 312, 325 (2008) (whereas "the experts at the FDA" apply a "cost-benefit analysis," a jury "sees only the cost of a more dangerous design, and is not concerned with its benefits; the patients who reaped those benefits are not represented in court"); 150 Cong. Rec. S8657-01 (daily ed. July 22, 2004) (statement of former FDA Chief Counsels) ("If every state judge and jury could fashion their own labeling requirements for drugs and medical devices, . . . FDA's ability to advance the public health by allocating

scarce space in product labeling to the most important information would be seriously eroded.").

CONCLUSION

The petition for a writ of certiorari should be granted.

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RECORD AND BRIEFS

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In The Supreme Court of the United States

MERCK SHARP & DOHME CORP.,

Petitioner,

v.

DORIS ALBRECHT, ET AL.,

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Third Circuit

BRIEF OF THE PRODUCT LIABILITY ADVISORY COUNCIL, INC. AND THE CHAMBER OF COMMERCE OF THE UNITED STATES OF AMERICA AS *AMICI CURIAE* IN SUPPORT OF PETITIONER

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BRIEF OF THE PRODUCT LIABILITY ADVISORY COUNCIL, INC. AND THE CHAMBER OF COMMERCE OF THE UNITED STATES OF AMERICA AS *AMICI CURIAE* IN SUPPORT OF PETITIONER

INTEREST OF THE *AMICI CURIAE*[1]

The Product Liability Advisory Council, Inc. (PLAC) is a non-profit corporation with 90 corporate members representing a broad cross-section of American industry. Its corporate members include manufacturers and sellers of a variety of products, including automobiles, trucks, aircraft, electronics, cigarettes, tires, chemicals, pharmaceuticals, and medical devices. (A list of PLAC's corporate members is appended to this brief.) PLAC's primary purpose is to file *amicus curiae* briefs in cases that raise issues affecting the development of product liability litigation and have potential impact on PLAC's members.

The Chamber of Commerce of the United States of America (the "Chamber") is the world's largest business federation. It represents 300,000 direct

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[1] Letters of consent from all parties to the filing of this brief have been lodged with the Clerk. Pursuant to S. Ct. Rule 37.2, PLAC and the Chamber state that all parties' counsel received timely notice of the intent to file this brief. Pursuant to S. Ct. Rule 37.6, *amici* state that no counsel for a party wrote this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity, other than the *amici curiae*, their members, or their counsel, has made a monetary contribution to this brief's preparation or submission.

members and indirectly represents the interests of more than three million companies and professional organizations of every size, in every industry sector, from every region of the country. An important function of the Chamber is to represent the interests of its members in matters before Congress, the Executive Branch, and the courts. To that end, the Chamber regularly files *amicus* briefs in cases that raise issues of vital concern to the Nation's business community.

This is such a case. It presents an important question that has produced uncertainty and serious confusion in the lower courts involving the scope of implied conflict preemption in the aftermath of this Court's decision in *Wyeth* v. *Levine*, 555 U.S. 555 (2009). PLAC, the Chamber, and their members have a vital interest in the proper resolution of the question presented.

STATEMENT

1. *The Supremacy Clause and Conflict Preemption.* State and local laws that conflict with federal law are preempted "by direct operation of the Supremacy Clause." *Brown* v. *Hotel & Restaurant Employees & Bartenders Int'l Union Local 54*, 468 U.S. 491, 501 (1984). Although this Court sometimes has separately discussed "impossibility," "obstacle" and ordinary "conflict" preemption, these "terminological" distinctions cannot obscure the fundamental principle that the Supremacy Clause reaches *all* cases where there is an *actual* or *direct* conflict between state and federal requirements. *Geier* v. *Am. Honda Motor Co.*, 529 U.S. 861, 873-74 (2000); see also *Hines* v. *Davidowitz*, 312 U.S. 52, 67

(1941) (discussing wide range of verbal formulations in Court's many cases involving conflict preemption).

The Supremacy Clause serves a vital structural role in our Nation's government by protecting federal law and programs against encroachment and interference by subordinate governments. It also helps to create unified and rational markets for nationally distributed goods and services by ensuring that uniform federal regulation – often the product of expert agency decision-making pursuant to authority delegated by Congress – is not undermined or subverted by state or local law, including state tort law as applied by lay juries. And it ensures that regulated persons, businesses, and other entities are not placed in the impossible position of being compelled to obey directly conflicting legal obligations imposed by federal and state law.

2. *Wyeth* v. *Levine*. In *Wyeth*, this Court addressed the preemptive effect of the Federal Food, Drug and Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.*, associated federal regulations relating to drug labeling, and regulatory action by the FDA, on state-law failure-to-warn claims brought against manufacturers of prescription drugs. Federal law, the Court explained, does not preempt such state-law claims if applicable regulations would have allowed the manufacturer unilaterally to alter its previously approved labeling and ultimately FDA would have approved that change, but does preempt if FDA would have rejected that change. 555 U.S. at 568, 570-71 (discussing "Changes Being Effected" (CBE) regulation), 21 C.F.R. § 314.70(c)). When defendant asserted FDA "intended to prohibit it from strengthening the warning" and would have rejected

the warning change proposed by plaintiff, the state courts rejected that contention "as a matter of fact," and this Court affirmed the resulting no-preemption ruling, concluding the record did not contain "clear evidence" supporting defendant's contention; in fact, it contained "*no* evidence . . . that either the FDA or the manufacturer gave more than passing attention to" the risks in question. *Id.* at 572 & n.5 (internal quotation marks omitted; emphasis added).

3. *The Decisions Below.* This case arises out of a multi-district litigation (MDL) involving more than a thousand state-law tort actions, including claims for failure to warn, brought against petitioner Merck Sharpe & Dohme Corp. (Merck), which manufactures an osteoporosis drug called Fosamax. Among other things, plaintiffs claimed Merck should have provided a stronger warning concerning the risk of certain bone fractures.

Following a bellwether trial – and based on a painstaking analysis of "a complete record" (including extensive documentary and other evidence regarding FDA's oversight and regulation of the labeling) – the district court concluded "preemption is warranted because there is clear evidence that the FDA would not have approved a change to the Precautions section of the Fosamax label prior to" plaintiff's injury. Pet. App. 164a, 168a, 169a-174a; see also *id.* at 156a-162a, 168a-174a.

The Third Circuit vacated and remanded. Pet. App. 1a-95a. Parting company with other courts, it held that *Wyeth*'s unelaborated reference to "clear evidence" was meant to impose on the defendant manufacturer a heightened standard of proof akin to the "clear and convincing evidence" test under which

defendant must prove that FDA would have rejected the proposed warning change. Breaking additional new ground, the Third Circuit also ruled that whether FDA would have rejected a warning is a question *for the jury*, even where as here the historical facts are undisputed, and therefore a manufacturer cannot prevail pre-trial, as a matter of law, unless there is a "smoking gun" FDA rejection letter from which a jury could only find the claim preempted. Pet. App. 36a-37a, 54a-55a. Based on those demanding standards, the court of appeals opined that a reasonable jury "could conclude" that FDA would have allowed the labeling change sought by plaintiffs (even though FDA had in fact *rejected* proposed warning language concerning the very risk in question). *Id.* at 67a. The court remanded so juries in individual cases could decide, following a full trial, what FDA would have done.

INTRODUCTION AND SUMMARY OF ARGUMENT

This case raises a recurring and significant question of federal law – and the meaning of the Supremacy Clause – that has vexed and confused the lower courts and is of paramount importance to the pharmaceutical industry. The federal and state courts are deeply confused over the meaning of certain language in *Wyeth* v. *Levine*, 555 U.S. 555 (2009) – specifically, this Court's statement that, while an "impossibility" preemption defense was not available on the particular record developed there, it would have been available if there had been "clear evidence" FDA would have rejected the warning sought by plaintiff. *Id.* at 571. In the decision below, the Third Circuit has adopted a novel gloss on those

two words in *Wyeth* that erects an exceedingly high – and unwarranted – barrier to the use of conflict preemption arguments by pharmaceutical manufacturers. Because only this Court can clarify what it meant in *Wyeth*, further review is needed.

I. The lower courts are confused and sharply divided over the meaning of *Wyeth*'s unelaborated reference to "clear evidence." The Third Circuit candidly acknowledged as much, noting that the meaning of that phrase on its face was "cryptic" and the "lower courts have struggled to make it readily administrable." Pet. App. 28a. The court of appeals also observed that at least two different approaches had been developed in the lower courts, one "more complex" than the other – and then proceeded to reject both in favor of a third reading. *Id.* at 33a-35a; see also *id.* at 35a (concluding that "clear evidence" "does not refer directly to the *type* of facts that" must be demonstrated, "or to the circumstances in which preemption will be appropriate" but rather to "how *difficult* it will be for the manufacturer to convince the factfinder"). In holding that *Wyeth* "intended to announce" a "standard of proof" requiring "clear and convincing" evidence (Pet. App. 35a, 37a), the Third Circuit misread this Court's opinion and parted company with other federal and state decisions.

Indeed, the law in this area is so confused that courts have reached conflicting outcomes on virtually identical regulatory records just as the circuit and district courts did here. Compare, *e.g.*, *Robinson* v. *McNeil Consumer Healthcare*, 615 F.3d 861, 869-70, 873 (7th Cir. 2010) (upholding preemption for Children's Motrin label) with *Reckis* v. *Johnson & Johnson*, 28 N.E.3d 445, 457 (Mass. 2015) (rejecting

preemption). Beyond that, there are numerous tertiary or subsidiary disagreements in the lower courts over precisely what this Court meant by or what qualifies as "clear evidence." Courts and commentators alike have recognized and bemoaned this state of confusion and many have strongly suggested the need for clarification from this Court.

This case presents a valuable opportunity not only to resolve the lower courts' confusion but also to bring greater coherence to federal preemption law. Contrary to the Third Circuit's view, *Wyeth* did not invent a novel, virtually insurmountable burden of proof. Instead, this Court's reference to "clear evidence" merely reflects well-settled precedent establishing that conflict preemption in every form requires demonstration of an *actual*, rather than merely a hypothetical or potential, conflict between federal and state law. See, *e.g.*, *Geier* v. *Am. Honda Motor Co.*, 529 U.S. 861, 884-85 (2000) (conflict preemption "turns on the identification of [an] 'actual conflict[]'" and should not be found "too readily in the absence of *clear evidence* of a *conflict*") (emphasis added); *English* v. *General Electric Co.*, 496 U.S. 72, 90 (1990) (rejecting conflict preemption argument where conflict was "too speculative"). Indeed, *Geier* specifically *rejected* as unworkable and unwieldy a proposal to impose on defendants a "special burden" to establish preemption. In erroneously equating *Wyeth*'s statements with a "clear and convincing" standard of proof, the Third Circuit ignored the origins of the "clear evidence" language in this Court's preemption cases, referring instead to various non-preemption settings that are readily distinguishable. See Pet. 26-27. The Third Circuit also ignored the procedural posture of *Wyeth*, in

which the Court would not have rejected the state courts' factual findings absent "extraordinary" circumstances (*i.e.*, "clear evidence" that those findings were erroneous).

Further review would permit this Court to clarify the nature of the inquiry courts must undertake to determine whether FDA would have approved a labeling change. As petitioner correctly points out, this case is an ideal vehicle for "putting another stake in the ground" that contrasts with *Wyeth* and articulates "an administrable rule of law that *protects* the Supremacy Clause," because petitioner "presented compelling evidence on every front where Wyeth fell short." Pet. 34; *id.* at 28. At the end of the day, only this Court can clarify what it meant by "clear evidence."

II. Review is also warranted because the Third Circuit's flawed approach, if permitted to stand, would create serious negative consequences. The court of appeal's decision deprives litigants of the recognized benefits of preemption as a case-dispositive issue that can be resolved prior to trial; ignores this Court's teachings in both *PLIVA, Inc.* v. *Mensing*, 131 S. Ct. 2567 (2011), and *Mutual Pharmaceutical Co.* v. *Bartlett*, 133 S. Ct. 2466 (2013); creates perverse incentives for manufacturers to burden FDA with constant proposed labeling changes for preemption purposes (an institutional burden this Court declared was important in *Buckman Co.* v. *Plaintiffs' Legal Committee*, 531 U.S. 341 (2001)); and threatens to inhibit drug development by imposing massive additional litigation costs on drug manufacturers in the rising tide of product liability litigation against them. To

avoid these adverse effects, the petition should be granted.

ARGUMENT

I. REVIEW IS NEEDED TO RESOLVE CONFLICTS AND CONFUSION IN THE LOWER COURTS AND CLARIFY *WYETH*'S REFERENCE TO "CLEAR EVIDENCE"

A. The Decision Below Compounds The Confusion In The Lower Courts

As the Third Circuit itself recognized (Pet. App. 33a-36a), there is rampant confusion in the lower courts over the meaning of *Wyeth*'s reference to "clear evidence." The court correctly noted that the meaning of this language, on its face, was "cryptic" and the "lower courts have struggled to make it readily administrable." Pet. App. 28a. The Third Circuit also stated that at least two different approaches had been developed in the lower courts, one "more complex" than the other – and then proceeded to reject both in favor of yet a third reading. *Id.* at 33a-35a; see also *id.* at 35a (concluding that "clear evidence" "does not refer directly to the *type* of facts that" must be demonstrated, "or to the circumstances in which preemption will be appropriate," but rather to "how *difficult* it will be for the manufacturer to convince the factfinder").

The confusion, however, extends well beyond that recognized by the Third Circuit. For example, on the same record involving the same warning for Children's Motrin, the Seventh Circuit and Massachusetts Supreme Judicial Court (SJC) have

reached diametrically opposed conclusions regarding conflict preemption. Compare *Robinson* v. *McNeil Consumer Healthcare*, 615 F.3d 861, 869-70, 873 (2010) (concluding there was "clear evidence" FDA would have rejected proposed warning change) with *Reckis* v. *Johnson & Johnson*, 28 N.E.3d 445, 457-60 (Mass. 2015) (reaching opposite conclusion). Such conflicting outcomes necessarily reflect divergent understandings of what is required by *Wyeth*'s reference to "clear evidence" (just as do the conflicting decisions of the circuit and district courts in this case).

What is more, there are multiple tertiary disagreements – and much confusion – in the lower courts over precisely what qualifies as "clear evidence." Compare, *e.g.*, *Aaron* v. *Wyeth*, 2010 WL 653984, at *6 (W.D. Pa. Feb 19, 2010) (holding manufacturer's proposal to FDA to add warning and FDA's rejection of proposal not "clear evidence" because manufacturer "did not press its position" but "acquiesced" in FDA decision) with *Dobbs* v. *Wyeth Pharmaceuticals*, 797 F. Supp. 2d 1264, 1279 (W.D. Okla. 2011) ("This court disagrees with *Aaron*'s interpretation of the proof standard announced in [*Wyeth*]."). Some courts, in upholding preemption, have relied on FDA's rejection of warnings proposed by *citizen petitions* rather than by the manufacturer under the CBE regulation, whereas others have insisted on the latter. Compare, *e.g.*, *Cerveny* v. *Aventis, Inc.*, 855 F.3d 1091, 1099, 1102 (10th Cir. 2017) (finding "clear evidence" where FDA rejected warning proposed by citizen petition and rejecting argument FDA "accord[s] greater deference to changes proposed by manufacturers than [by]. . .citizen[s]") and *Dobbs*, 797 F. Supp. at 1274

(finding clear evidence based on FDA rejection of citizen petition) with *Reckis*, 28 N.E.3d at 457-60 (concluding FDA's rejection of warnings proposed by citizen petition did not show that agency would have rejected same warning if *manufacturer* had proposed it) and *Baumgardner* v. *Wyeth Pharmaceuticals*, 2010 WL 3431671, at *1 (E.D. Pa. Aug. 31, 2010) (same). See also Thomas Ayala & Elizabeth Graham, *Overcome the Clear Evidence Defense*, 52 Trial 32, 34 & nn. 13-16 (July 2016) (acknowledging this split of authority and discussing additional cases).

These tertiary disagreements exist among those courts that have assumed, contrary to the Third Circuit's holding, that "clear evidence" refers either to "the *type* of facts that" must be demonstrated "or to the circumstances in which preemption will be appropriate," not to "how *difficult* it will be for the manufacturer to convince the factfinder." Pet. App. 35a. The Third Circuit's decision to adopt a "clear and convincing" standard of proof only compounds this confusion.[2] Not surprisingly, many commentators have also recognized the widespread confusion and conflicts in the lower courts. See, *e.g.*,

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[2] The misunderstanding of how the conflict preemption inquiry should be conducted is also reflected in the suggestion of various lower courts that preemption cannot be established unless a manufacturer *actually proposes* the allegedly missing warning, the FDA *actually rejects the manufacturer's proposal*, or both. Requiring such proof denies preemption in precisely those cases involving the most scientifically unfounded warnings, which *no* manufacturer would ever propose (and FDA *unquestionably* would reject). That cannot possibly be the law, nor can it be what this Court meant in *Wyeth*.

Ayala & Graham, *supra*, 52 Trial at 34 & nn. 13-16; Michael Gallagher, *Clear Evidence of Impossibility Preemption After Wyeth v. Levine*, 51 GONZ. L. REV. 439, 440-42 (2015-2016) ("neither courts nor litigants nor commentators know exactly what clear evidence means" and "[c]ourts have issued divergent opinions").

The lower courts have repeatedly noted the absence of and/or need for further guidance from this Court concerning what qualifies as "clear evidence" in this important and recurring setting. See, *e.g.*, *Mason* v. *Smithkline Beecham Corp.*, 596 F.3d 387, 391 (7th Cir. 2010) (because *Wyeth* "did not clarify what constitutes 'clear evidence[,]' . . . the only thing we know for sure" is that the evidence in that case "did not meet" that "standard"); *Dobbs*, 797 F. Supp. 2d at 1270 (noting that "'lower courts are left to determine what satisfies this 'clear evidence' standard'") (quoting *Schilf* v. *Eli Lilly & Co.*, 2010 WL 3909909, at *4 (D.S.D. Sept. 30, 2010)). It is time to heed this call.

B. The Third Circuit Misunderstood *Wyeth*'s Reference To "Clear Evidence"

In the absence of clearer guidance from this Court, the Third Circuit – along with some other courts – have concluded that this Court's reference to "clear evidence" was intended to require more than a mere preponderance of the evidence. The Third Circuit expressly adopted the "clear and convincing" standard of proof, whereas other courts have used different formulations that may or may not be even more demanding. Pet. App. 35a, 37a. See, *e.g.*, *Mason*, 596 F.3d at 391 (describing "clear evidence"

as an "exacting" and "stringent" standard); *Forst* v. *Smithkline Beecham Corp.*, 639 F. Supp. 2d 948, 953 (E.D. Wis. 2009) (under *Wyeth* "a defendant drug manufacturer faces an exacting burden"). But in concluding that "clear evidence" was really "clear *and convincing*" evidence, the Third Circuit relied largely on various non-preemption decisions of this Court that, as petitioner demonstrates, are all readily distinguishable. See Pet. 26-27; Pet. App. 36a-37.

Tellingly, however, the Third Circuit failed to take account of this Court's *conflict preemption* decisions that have articulated the need for "clear evidence" in that setting. Had the Third Circuit done so, it would have recognized that, far from announcing a novel and "exacting" new standard of proof, *Wyeth*'s reference to "clear evidence" merely reflects and expresses well-settled and longstanding principles involving conflict preemption.

Federal preemption is usually raised as an affirmative defense. And in civil actions, the ordinary or default burden of persuasion is proof by a preponderance of the evidence.[3] Thus, a defendant ordinarily must prove any facts necessary for a preemption defense by a preponderance of the

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[3] Although preemption is a *legal* defense, sometimes (as in this setting) the defense can hinge on case-specific regulatory facts and circumstances. In every conflict preemption case, however, a court (1) ascertains the meaning of state law; (2) determines the meaning of federal law; and (3) makes a judgment whether the former conflicts with, or serves as an obstacle to, the latter. *Perez* v. *Campbell*, 402 U.S. 637, 644 (1971).

evidence.[4] In a long line of cases, this Court has made clear that ordinarily the proponent of a conflict preemption defense must demonstrate an *actual* conflict between state and federal law – potential or hypothetical conflicts are not enough. The preemptive conflict, in other words, must be "clear." See, *e.g.*, *Geier* v. *Am. Honda Motor Co.*, 529 U.S. at 861, 884 (2000) (conflict preemption "turns on the identification of 'actual conflict[]'"); *English* v. *General Electric Co.*, 496 U.S. 72, 90 (1990) (rejecting conflict preemption argument where claimed conflict was "too speculative"); *Rice* v. *Norman Williams Co.*, 458 U.S. 654, 664 (1982) (Court's decisions "enjoin seeking out conflicts between state and federal regulation where none *clearly* exists") (emphasis added; quotation marks omitted). "Clear evidence" in this setting thus means what it always has meant:

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[4] Courts and commentators have suggested that, in cases such as this, the burden of proof ought to be placed on plaintiff in whole or at least in part. See David Geiger & Andrew London, *Wyeth's "Clear Evidence" Language: Clearly Misunderstood*, Law360 (Jan. 12, 2016) (arguing that, in light of the federal regulatory scheme, plaintiff should bear the burden to prove what constitutes an exception to the preemption that would otherwise exist once defendant proved it was using FDA-approved labeling); *Utts* v. *Bristol-Myers Squibb Co.*, 2017 WL 1906875, at *9, *19 (S.D.N.Y. May 18, 2007) (only after plaintiff "prove[s] the existence of newly acquired information" allowing a manufacturer to submit a CBE does burden shift to manufacturer to show that FDA would have rejected labeling change). And this Court has made clear that preemption is not always "in the nature of an affirmative defense." *Int'l Longshoremen's Ass'n* v. *Davis*, 476 U.S. 380, 381-82, 387-89 (1986) (involving so-called "*Garmon*" preemption under the National Labor Relations Act). Further review would allow the Court to clarify how the burden of proof operates in cases such as this.

the demonstration of an *actual*, as opposed to merely a *potential*, conflict.

This reading is amply confirmed by *Geier*, which also used the "clear evidence" formulation in evaluating proof of conflict preemption. Specifically, this Court in *Geier* reasoned that conflict preemption "turns on the identification of 'actual conflict[]'" and then explained that "a court should not find pre-emption too readily in the absence of *clear evidence* of a *conflict*." 529 U.S. at 884-85 (emphasis added).

In referring to "clear evidence," the Court in *Geier* cited a portion of its previous decision in *English*. The relevant portion of *English* addressed whether administrative anti-retaliation provisions for employees in the nuclear power industry, established by a federal statute, preempted emotional distress tort claims under state law. Rejecting the argument that Congress's inclusion of "expeditious time-frames" in the federal administrative remedy preempted state claims with longer deadlines, the Court expressed skepticism that without preemption "employees will forgo their [federal administrative] options and rely solely on state remedies for retaliation." *English*, 496 U.S. at 89-90. "Such a prospect," the Court explained,

> is simply *too speculative* a basis on which to rest a finding of pre-emption. The Court has observed repeatedly that pre-emption is ordinarily not to be implied absent an 'actual conflict.' See, *e.g.*, *Savage* v. *Jones*, 225 U.S. 501, 533 (1912). The 'teaching of this Court's decisions . . . enjoin[s] seeking out conflicts between state and federal regulation where none

> *clearly* exists.' *Huron Portland Cement Co.* v. *Detroit*, 362 U.S. 440, 446 (1960).

Id. at 90 (emphasis added). The references to "clear evidence" in *Geier* and "clear" conflicts in *English* are thus nothing more than a restatement of the basic principle that, for the Supremacy Clause to come into play, there must be an "actual," and not merely a potential, conflict between federal and state requirements.

Nor is this all. If the Court in *Wyeth* had meant more than the "clear" evidence required in *Geier* and *English* – if it had meant to create a special new ("clear and convincing" or "exacting") standard of proof unique to prescription drug labeling cases – then it surely would have said so. The Court, like Congress, "does not . . . hide elephants in mouseholes." *Whitman* v. *Am. Trucking Ass'ns., Inc.*, 531 U.S. 457, 468 (2001).

The Third Circuit's reading of *Wyeth* is especially implausible for at least two additional reasons. First, in *Geier* the Court expressly *rejected* an argument that a defendant must shoulder a "special burden" of proof in certain subcategories of implied preemption cases. 529 U.S. at 870-74. Such a "special burden," the Court explained in words that are equally applicable to the Third Circuit's holding, "find[s]" no "basis . . . in this Court's precedents" and would "promise practical difficulty by further complicating well-established pre-emption principles that already are difficult to apply." *Id.* at 872-73. In light of that holding, *Geier*'s reference to "clear evidence" obviously did not alter the ordinary burden of establishing a preemption defense. Nor is it plausible to conclude that the Court in *Wyeth*

intended to adopt the very kind of "special burden" rejected in *Geier* (without even mentioning this aspect of that decision).

Second, the Third Circuit's suggestion that *Wyeth* intended to create a "clear and convincing" proof standard (even though that issue was neither raised nor briefed there) overlooks the procedural posture of that case. In *Wyeth*, the Court was evaluating the drug manufacturer's argument in light of factual findings made by two lower state courts, including that (1) certain warnings rejected by FDA were not materially different from the allegedly defective warning that actually accompanied the product, and (2) FDA did not intend to prohibit the manufacturer from strengthening the warning. See 555 U.S. at 572 & n.5. This Court's statement that there must be "clear evidence" was no doubt informed by this procedural posture and what would be necessary to overcome the state courts' factual findings. See *324 Liquor Corp.* v. *Duffy*, 479 U.S. 335, 351 (1987) (this Court "customarily accept[s] the factual findings of state courts in the absence of exceptional circumstances"); see also Geiger & London, *supra*, Law360 ("'clear evidence' language was necessitated by the fact that the preemption issue turned on factual findings made by the Vermont courts, which the Supreme Court could not ordinarily reverse absent exceptional circumstances").

Further review would allow this Court to clarify that *Wyeth* did not intend to adopt a "clear and convincing" (or for that matter a "stringent" or "exacting") standard of proof unique to pharmaceutical cases. It would also permit the

Court to resolve some of the tertiary disagreements in the lower courts described above, by making clear that *any* type of proof showing by a preponderance of the evidence that FDA would have rejected a warning (including, for example, a rejected citizen petition) can qualify as "clear evidence."

C. Only This Court Can Clarify What It Meant in *Wyeth*

At bottom, the serious confusion in the lower courts stems from this Court's unelaborated reference in *Wyeth* to "clear evidence." For that reason, further litigation in the lower courts is unlikely to lead to greater clarity. Instead, as the experience since *Wyeth* confirms, it will only produce greater confusion and uncertainty. The Third Circuit's decision is illustrative: it only adds new and different approaches and deepens the confusion.

As this Court has recognized, the law of federal preemption is complicated and "difficult to apply." *Geier*, 529 U.S. at 873. Some of this Court's preemption decisions have featured multiple opinions that combine to form the Court's majority. See, *e.g.*, *Medtronic, Inc.* v. *Lohr*, 518 U.S. 470 (1996); *Cipollone* v. *Liggett Group, Inc.*, 505 U.S. 504 (1992). When ambiguities in those decisions have led to conflicting interpretations and confusion in the lower courts, this Court has not hesitated to step in to restore uniformity. See, *e.g.*, *Freightliner* v. *Myrick*, 514 U.S. 280, 288-89 (1995) (clarifying statement in *Cipollone* that had spawned lower court confusion regarding availability of implied preemption under statutes with express preemption clauses); *Geier*, 529 U.S. at 872-73 (discussing same).

The Court should do so here too. Ultimately, only this Court can offer definitive guidance on what it meant in *Wyeth*.

II. THE THIRD CIRCUIT'S DECISION IGNORES THIS COURT'S PRE-EMPTION TEACHINGS AND WILL CAUSE HARMFUL CONSEQUENCES

Not only did the Third Circuit impose on pharmaceutical manufacturers a demanding and unwarranted "clear and convincing evidence" burden of proof, but it also held that whether FDA would have rejected a proposed warning is a question for the jury, even when the historical facts are undisputed. Pet. App. 36a-37a, 46a-47a n.122, 54a-55a. As a consequence, conflict preemption will be relegated to a jury in situations even where, as here, the record clearly shows it is more likely than not that FDA would have rejected the proposed warning. See Pet. i, 28; Pet. App. 59a-60a. As well, under the decision below a manufacturer cannot prevail on the preemption defense pre-trial, as a matter of law, unless there is a "smoking gun" rejection letter from FDA that would leave a jury no choice but to find the state-law claim preempted. The Third Circuit's highly restrictive two-part gloss on *Wyeth* ignores this Court's teachings and, if permitted to stand, will have multiple adverse effects. For those reasons as well, review is warranted.

a. *Preemption's Value as a Threshold Legal Issue.* In most settings, courts treat preemption as a defense that is susceptible to being resolved on purely legal grounds at the threshold of or early in litigation (typically on a motion to dismiss or for

summary judgment). Cf. note 4, *supra*. Much of the practical benefit of the doctrine stems from its capacity to ensure that litigants are not forced to endure lengthy and costly discovery proceedings, and even trial, defending against state-law claims that violate the Supremacy Clause.

This Court has recognized the need to preserve this salutary function of preemption. For example, where preemption hinges on the allegations made in a complaint, the Court has repeatedly stated that plaintiffs may not avoid preemption through artful pleading. See, *e.g.*, *Aetna Health Inc.* v. *Davila*, 542 U.S. 200, 214 (2004) ("[D]istinguishing between pre-empted and non-pre-empted claims based on the particular label affixed to them would 'elevate form over substance and allow parties to evade' the pre-emptive scope of ERISA simply 'by relabeling their contract claims as claims for tortious breach of contract.'") (quoting *Allis-Chalmers Corp.* v. *Lueck*, 471 U.S. 202, 211 (1985)); *Chicago & N.W. Transp. Co.* v. *Kalo Brick & Tile Co.*, 450 U.S. 311, 324 (1981) ("[C]ompliance with the intent of Congress cannot be avoided by mere artful pleading."). But the Third Circuit's decision allows a litigant to avoid summary judgment merely by claiming that FDA's decision rejecting a warning concerning the risk in question might have been different if the warning had been worded only slightly differently. It is no more difficult to conjure up hypothetical alternative wordings for a warning than it is to use artful pleading in a complaint. See Pet. 23.

b. *This Court's Teachings in* PLIVA *and* Bartlett. This Court has not hesitated to *reject* speculative scenarios advanced by plaintiffs as

grounds for denying preemption. Illustrative are *PLIVA, Inc.* v. *Mensing*, 131 S. Ct. 2567 (2011), and *Mutual Pharmaceutical Co.* v. *Bartlett*, 133 S. Ct. 2466 (2013). Thus, in *PLIVA*, the Court rejected the argument that a generic drug manufacturer (which is obligated by federal law to use the same labeling as the brand-name drug) could have asked the FDA to change both its own and the brand-name label, and such a request might ultimately have resulted in FDA permission to change the generic-drug labeling. 131 S. Ct. at 2578-79. Because the manufacturer had not even *tried* to persuade the FDA to do so, the plaintiffs contended, the manufacturer could not establish conflict preemption. This Court emphatically rejected that argument, explaining that "[i]f these conjectures suffice to prevent federal and state law from conflicting for Supremacy Clause purposes," then conflict preemption would be rendered "largely meaningless." *Ibid.*

For exactly the same reason, this Court in *Bartlett* rejected plaintiff's contention that a drug manufacturer could avoid the direct conflict between federal and state law merely by electing to stop selling the medication altogether. See *Bartlett*, 133 S. Ct. at 2477 (accepting that argument would render impossibility preemption "meaningless"). The Third Circuit did not explain how its decision to relegate to *the jury* an equally speculative hypothetical scenario (notwithstanding all the record evidence here that FDA would have rejected the proposed warning) can be squared with *PLIVA* or *Bartlett*.

c. *Burdens on the FDA.* The Third Circuit's flawed approach would likely also burden the federal

regulatory process governing drug labeling. The decision below creates powerful incentives for drug manufacturers to constantly propose labeling changes to the FDA to ensure that plaintiffs cannot defeat preemption by invoking hypothetical alternative language.

In *Buckman Co.* v. *Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), which held that fraud-on-the-FDA claims are impliedly preempted, this Court emphasized the need to avoid such unwarranted burdens on FDA's regulatory processes. Specifically, the Court explained the negative impact such claims would have on the agency's approval of certain categories of medical devices:

> [F]raud-on-the-FDA claims would also cause applicants to fear that their disclosures to the FDA, although deemed appropriate by the Administration, will later be judged insufficient in state court. Applicants would then have an incentive to submit a deluge of information that the Administration neither wants nor needs, resulting in additional burdens on the FDA's evaluation of an application. As a result, the comparatively speedy [approval] process could encounter delays. . . .

531 U.S. at 351. In much the same way, the Third Circuit's flawed approach to conflict preemption will multiply the burdens on FDA's review process with respect to drug labeling.

d. *Effects on Drug Development and the Rising Tide of Pharmaceutical Litigation.* Developing drugs is very expensive. See, *e.g.*, J.A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New*

Estimates of R&D Costs, at 5 (Nov. 18, 2014) (estimated average industry cost of new prescription drug approval, inclusive of failures and capital costs, is $2.59 billion) (http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014..pdf). A manufacturer will not invest the vast sums necessary to develop a drug unless it believes it can recoup its investment. Allowing failure-to-warn claims to proceed under the varying tort laws of the fifty states despite a preponderance of the evidence that FDA would not have approved the proposed warnings would impose significant and unpredictable defense and liability costs on manufacturers, and thereby reduce their willingness to invest in developing new drugs. As the Tenth Circuit recently observed in the context of medical devices, "[r]equiring manufacturers to comply with fifty states' warning requirements ... on top of existing federal ... requirements, might introduce sufficient uncertainty and cost that manufacturers would delay or abandon at least some number of life-saving innovations." *Caplinger* v. *Medtronic, Inc.*, 784 F.3d 1335, 1346 (10th Cir. 2015) (Gorsuch, J.). The Third Circuit's decision will increase the costs and uncertainty of litigation faced by manufacturers by requiring more trials and placing the preemption issue in the hands of lay juries.

This is no idle concern. The extent of federal litigation against pharmaceutical companies, already immense, is rapidly expanding. The MDL proceedings in this case alone involve more than 1000 lawsuits. Moreover, in 2016 there were 21,517 product liability lawsuits filed against pharmaceutical companies in the federal courts, up from 6,791 just five years ago and 2,700 in 2001. See

Admin. Office of the U.S. Courts, Table C-2A: *U.S. District Courts--Civil Cases Commenced, by Nature of Suit, During the 12-Month Periods Ending September 30, 2012 Through 2016,* http://www.uscourts.gov/sites/default/files/data_tables/jb_c2a_0930.2016.pdf; Lisa Girion, *State Vioxx Trial Is Set as Drug Suits Boom,* L.A. Times, June 27, 2006, at C1. Today, out of seventy-three pending product liability MDL proceedings, twenty-eight, or *over 38%*, involve pharmaceuticals. See U.S. Judicial Panel on Multidistrict Litig., MDL Statistics Report – Distribution of Pending MDL Dockets by District (Aug. 15, 2017), http://www.jpml.uscourts.gov/sites/jpml/files/Pending_MDL_Dockets_By_District-August-15-2017.pdf. By comparison, between 1960 and 1999, there were only five MDL product liability actions involving FDA-approved medicines. See Deborah Hensler, *Has the Fat Lady Sung? The Future of Mass Toxic Torts,* 26 REV. LITIG. 883, 897-902 tbl. 1.1 (2007).

CONCLUSION

For the foregoing reasons, and those set forth in the petition for a writ of certiorari, the petition should be granted.

Respectfully submitted.

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SEPTEMBER 2017

APPENDIX

PRODUCT LIABILITY
ADVISORY COUNCIL, INC.
LIST OF CORPORATE MEMBERS

3M
Altec, Inc.
Altria Client Services Inc.
Astec Industries
Bayer Corporation
BIC Corporation
Biro Manufacturing Company, Inc.
BMW of North America, LLC
The Boeing Company
Bombadier Recreational Products, Inc.
Boston Scientific Corporation
Bridgestone Americas, Inc.
Bristol-Myers Squibb Corporation
C.R. Bard, Inc.
Caterpillar Inc.
CC Industries, Inc.
Celgene Corporation
Chevron Corporation
Cirrus Design Corporation
Continental Tire the Americas LLC
Cooper Tire & Rubber Company
Cordis Corporation
Crane Co.
Crown Equipment Corporation
Daimler Trucks North America LLC
Deere & Company
Delphi Automotive Systems
The Dow Chemical Company
E.I. duPont de Nemours and Company

Emerson Electric Co.
Exxon Mobil Corporation
FCA US LLC
Ford Motor Company
Fresenius Kabi USA, LLC
General Motors LLC
Georgia-Pacific LLC
GlaxoSmithKline
The Goodyear Tire & Rubber Company
Great Dane Limited Partnership
Hankook Tire America Corp.
Harley-Davidson Motor Company
The Home Depot
Honda North America, Inc.
Hyundai Motor America
Illinois Tool Works Inc.
Intuitive Surgical, Inc.
Isuzu North America Corporation
Jaguar Land Rover North America, LLC
Johnson & Johnson
Kawasaki Motors Corp., U.S.A.
Kia Motors America, Inc.
Kolcraft Enterprises, Inc.
Kubota Tractor Corporation
Lincoln Electric Company
Magna International Inc.
Mazak Corporation
Mazda Motor of America, Inc.
Medtronic, Inc.
Merck & Co., Inc.
Meritor WABCO
Michelin North America, Inc.
Microsoft Corporation
Mitsubishi Motors North America, Inc.
Mueller Water Products

Newell Brands Inc.
Novartis Pharmaceuticals Corporation
Novo Nordisk, Inc.
Pella Corporation
Pfizer Inc.
Polaris Industries, Inc.
Porsche Cars North America, Inc.
RJ Reynolds Tobacco Company
Robert Bosch LLC
The Sherwin-Williams Company
Sony Electronics Inc.
Stryker Corporation
Subaru of America, Inc.
TAMCO Building Products, Inc.
Teleflex Incorporated
Toyota Motor Sales, USA, Inc.
Trinity Industries, Inc.
The Viking Corporation
Volkswagen Group of America, Inc.
Volvo Cars of North America, Inc.
Wal-Mart Stores, Inc.
Western Digital Corporation
Whirlpool Corporation
Yamaha Motor Corporation, U.S.A.
Yokohama Tire Corporation
ZF TRW

No. 17-290

IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,

Petitioner,

v.

DORIS ALBRECHT, ET AL.,

Respondents.

On Writ of Certiorari
To The United States Court of Appeals
For The Third Circuit

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Exhibit 13 to Ecklund Declaration, 10/13/2010 Press Release, FDA Safety Communication: Safety update for osteoporosis drugs, bisphosphonates, and atypical fractures (Dkt. # 2996-13) (09/30/2013) *Molnar v. Merck & Co., Inc.*, No. 3:08-cv-00008-FLW-LHG 246

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Exhibit 15 to Ecklund Declaration, 06/13/2008 Email from J. Marchick, FDA Regulatory Project Manager, to J. Adams, U.S. Regulatory Liaison for Fosamax at Merck (Dkt. # 2996-15) (09/30/2013) *Molnar v. Merck & Co., Inc.*, No. 3:08-cv-00008-FLW-LHG 280

Exhibit 21 to Ecklund Declaration, E. Shane et al., *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research*, 25(11) J. Bone & Min. Res. 2267 (2010) (Dkt. # 2996-21) (09/30/2013) *Molnar v. Merck & Co., Inc.*, No. 3:08-cv-00008-FLW-LHG 283

Exhibit 45 to Ecklund Declaration, A. Neviaser et al., *Low-Energy Femoral Shaft Fractures Associated With Alendronate Use*, J. Orthop. Trauma, Vol. 22, No. 5 (2008) (Dkt. # 2996-45) (09/30/2013) *Molnar v. Merck & Co., Inc.*, No. 3:08-cv-00008-FLW-LHG 385

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Exhibit 48 to Ecklund Declaration,
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Exhibit 73 to Confoy Declaration, FDA Drug Safety Podcast — Podcast for Healthcare Professionals: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures, dated 03/17/2010 (Dkt. # 3035-73) (10/30/2013) *Molnar v. Merck & Co., Inc.*, No. 3:08-cv-00008-FLW-LHG 768

General Docket
Third Circuit Court of Appeals

Court of Appeals Docket #: 14-1900
Nature of Suit: 4365 Personal Injury-Product Liability In Re: Fosamax
Appeal From: United States District Court for the District of New Jersey
Fee Status: Paid
Docketed: 04/17/2014
Termed: 03/22/2017

* * *

Date Filed	Docket Text
	* * *
08/13/2015	ECF FILER: REDACTED CONSOLIDATED ELECTRONIC PROOF BRIEF with Volume I of Appendix attached on behalf of Appellant Doris Albrecht, filed. Certificate of Service dated 08/13/2015 by ECF.--[Edited 08/13/2015 by SLC]--[Edited 08/13/2015 by MS] (DCF) [Entered: 08/13/2015 10:52 AM]
10/28/2015	ECF FILER: ELECTRONIC PROOF BRIEF on behalf of Appellee Merck & Co Inc, filed. Certificate of Service dated 10/28/2015 by ECF. (JHB) [Entered: 10/28/2015 05:24 PM]
	* * *

11/04/2015	**ECF FILER: ELECTRONIC AMICUS/INTERVENOR BRIEF on behalf of Pharmaceutical Research and Manufacturers of America in support of Appellee/Respondent, filed. Certificate of Service dated 11/04/2015 by ECF. F.R.A.P. 29(a) Permission: YES. [Entry was mistakenly spread and has been removed from all other fosamax cases; modifier added]--[Edited 11/05/2015 by EMA]--[Edited 05/04/2016 by GPK removing PROOF from docket text.] (AWP) [Entered: 11/04/2015 04:32 PM]**
	* * *
12/21/2015	**ECF FILER: ELECTRONIC PROOF REPLY BRIEF on behalf of Appellant Doris Albrecht, filed. Certificate of Service dated 12/21/2015 by ECF. -- [Edited 01/06/2016 by EAF - Text edited to reflect Proof"] (DCF) [Entered: 12/21/2015 01:44 PM]**
	* * *
12/28/2015	**ECF FILER: ELECTRONIC APPENDIX on behalf of Appellant Doris Albrecht, filed. Certificate of service dated 12/28/2015 by ECF. (DCF) [Entered: 12/28/2015 12:11 PM]**

12/28/2015	**ECF FILER: ELECTRONIC APPENDIX on behalf of Appellant Doris Albrecht, filed. Certificate of service dated 12/28/2015 by ECF. (DCF) [Entered: 12/28/2015 12:14 PM]**
12/28/2015	**ECF FILER: ELECTRONIC APPENDIX on behalf of Appellant Doris Albrecht, filed. Certificate of service dated 12/28/2015 by ECF. (DCF) [Entered: 12/28/2015 12:16 PM]**
12/28/2015	**ECF FILER: REDACTED ELECTRONIC APPENDIX on behalf of Appellant Doris Albrecht, filed. Certificate of service dated 12/28/2015 by ECF. (DCF) [Entered: 12/28/2015 12:18 PM]**
12/29/2015	**HARD COPY RECEIVED from Appellant Doris Albrecht - Appendix. Copies: 4. Volumes: 2 - 5 (Volume 5 received - REDACTED and UNDER SEAL) (EAF) [Entered: 12/31/2015 03:05 PM]**
	* * *
01/11/2016	**ECF FILER: REDACTED ELECTRONIC BRIEF with Volume I of Appendix attached on behalf of Appellant Doris Albrecht, filed. Certificate of Service dated**

	01/11/2016 by ECF. (DCF) [Entered: 01/11/2016 10:15 AM]
	* * *
01/12/2016	HARD COPY RECEIVED from Appellant Doris Albrecht - Reply Brief. Copies: 7. (SJB) [Entered: 01/12/2016 11:05 AM]
01/12/2016	HARD COPY RECEIVED from Appellee Merck & Co Inc - Brief. Copies: 7. (NON-COMPLIANT)-- [Edited 01/21/2016 by EMA] (SJB) [Entered: 01/12/2016 11:07 AM]
01/12/2016	HARD COPY RECEIVED from Appellant Doris Albrecht - Brief with Volume I of Appendix attached. Copies: (FILED UNDER SEAL) (SJB) [Entered: 01/12/2016 11:25 AM]
01/12/2016	HARD COPY RECEIVED from Appellant Doris Albrecht - REDACTED Brief with Volume I of Appendix attached. Copies: 7. (SJB) [Entered: 01/12/2016 11:27 AM]
	* * *
01/27/2016	HARD COPY RECEIVED from Appellee Merck & Co Inc - Brief. Copies: 7. (KEL) [Entered: 01/27/2016 11:27 AM]
	* * *

03/22/2017	PRECEDENTIAL OPINION Coram: FUENTES, CHAGARES and RESTREPO, Circuit Judges. Total Pages: 89. Judge: FUENTES Authoring. (SLC) [Entered: 03/22/2017 07:37 AM]
03/22/2017	JUDGMENT, Reversed and Remanded. Costs shall not be taxed. (SLC) [Entered: 03/22/2017 07:39 AM]
	* * *
04/24/2017	ORDER (SMITH, Chief Judge, AMBRO, CHAGARES, JORDAN, HARDIMAN, VANASKIE, SHWARTZ, KRAUSE, RESTREPO and *FUENTES, Circuit Judges) denying Petition for En Banc and for Panel Rehearing filed by Appellee Merck & Co Inc, filed. FUENTES, Authoring Judge. (*Judge Fuentes vote is limited to panel rehearing only.) (CJG) [Entered: 04/24/2017 01:38 PM]
05/01/2017	MANDATE ISSUED, filed. (Resent with correct appendix)--[Edited 05/01/2017 by SLC] (SLC) [Entered: 05/01/2017 07:18 AM]
	* * *

U.S. District Court
District of New Jersey [LIVE] (Trenton)
CIVIL DOCKET FOR CASE #: 3:12-cv-05485-FLW-LHG

KNOPICK et al v. MERCK & CO. et al
Assigned to: Judge Freda L. Wolfson
Referred to: Magistrate Judge Lois H. Goodman
Lead case: 3:08-cv-00008-FLW-LHG
Member case: (View Member Case)
Cause: 28:1332 Diversity-Product Liability
Date Filed: 08/31/2012
Date Terminated: 06/13/2018
Jury Demand: Plaintiff
Nature of Suit: 365 Personal Inj. Prod. Liability
Jurisdiction: Diversity

In Re

FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (NO. II)

* * *

Date Filed	#	Docket Text
08/31/2012	1	COMPLAINT against MERCK & CO., MERCK SHARPE & DOHME CORP. (Filing fee $ 350 receipt number 4549895) with JURY DEMAND, filed by CAROL KNOPICK. (Attachments: # 1 Civil Cover Sheet)(jjc) (Entered: 08/31/2012)

* * *

U.S. District Court
District of New Jersey [LIVE] (Trenton)
CIVIL DOCKET FOR CASE #: 3:12-cv-01275-JAP-LHG

STEVES et al v. MERCK SHARPE & DOHME et al
Assigned to: Judge Joel A. Pisano
Referred to: Magistrate Judge Lois H. Goodman
Lead case: 3:08-cv-00008-FLW-LHG
Member case: (View Member Case)
Cause: 28:1332 Diversity-Product Liability
Date Filed: 03/01/2012
Date Terminated: 12/17/2014
Jury Demand: Plaintiff
Nature of Suit: 365 Personal Inj. Prod. Liability
Jurisdiction: Diversity

In Re

FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (NO. II)

* * *

Date Filed	#	Docket Text
03/01/2012	1	COMPLAINT against MERCK SHARPE & DOHME, NORTHSTAR RX, LLC, PHARMACEUTICALS, INC., SANOFI-AVENTIS, U.S., INC., SANOFI-AVENTIS, U.S., LLC, TEVA PHARMACEUTICALS USA, INC., WARNER CHILCOTT (US), LLC (Filing fee $ 350 receipt number 4212913.) JURY DEMAND., filed by JAMES

STEVES, SUSAN STEVES.(jjc)
(Entered: 03/02/2012)

* * *

U.S. District Court
District of New Jersey [LIVE] (Trenton)
CIVIL DOCKET FOR CASE #:
3:11-cv-05304-JAP-LHG

GLYNN et al v. MERCK SHARP & DOHME CORP.
Assigned to: Judge Joel A. Pisano
Referred to: Magistrate Judge Lois H. Goodman
Lead case: 3:08-cv-00008-FLW-LHG
Member case: (View Member Case)
Cause: 28:1332 Diversity-Product Liability
Date Filed: 09/15/2011
Date Terminated: 06/27/2013
Jury Demand: Plaintiff
Nature of Suit: 365 Personal Inj. Prod. Liability
Jurisdiction: Diversity

In Re

FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (NO. II)

* * *

Date Filed	#	Docket Text
		* * *
01/15/2013	26	DECLARATION of Karen A. Confoy in Support of Merck's Motion for Summary Judgment and Motion for Summary Judgment Based Upon Federal Preemption re 25MOTION for Summary Judgment *Based Upon Federal Preemption*, 24 MOTION for Summary Judgment by

MERCK SHARP & DOHME CORP.. (Attachments: # 1 Ex. 1, # 2 Ex. 2, # 3 Ex. 5, # 4 Ex. 7, # 5 Ex. 9, # 6 Ex. 13, # 7 Ex. 14, # 8 Ex. 15, # 9 Ex. 16, # 10 Ex. 17, # 11 Ex. 19, # 12 Ex. 20, # 13 Ex. 22, # 14 Ex. 23, # 15 Ex. 25, # 16Ex. 26, # 17 Ex. 31, # 18 Ex. 32, # 19 Ex. 33, # 20 Ex. 36, # 21 Ex. 41)(CONFOY, KAREN) (Entered: 01/15/2013)

* * *

04/29/2013 213 JURY VERDICT FORM. (dm) (Entered: 04/30/2013)

* * *

U.S. District Court
District of New Jersey [LIVE] (Trenton)
CIVIL DOCKET FOR CASE #: 3:08-cv-00008-FLW-LHG

MOLNAR et al v. MERCK & CO., INC.
Assigned to: Judge Freda L. Wolfson
Referred to: Magistrate Judge Lois H. Goodman
Cause: 28:1332 Diversity-Product Liability
Date Filed: 01/02/2008
Date Terminated: 06/27/2013
Jury Demand: Plaintiff
Nature of Suit: 367 Personal Injury: Health Care/Pharmaceutical Personal Injury Product Liability
Jurisdiction: Diversity

In Re

FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (NO. II)

* * *

Date Filed	#	Docket Text
		* * *
07/14/2011	113	CASE MANAGEMENT ORDER NO. 4. Signed by Chief Judge Garrett E. Brown, Jr on 7/14/2011. (eaj) (Main Document 113 replaced on 7/15/2011) (mmh). (Entered: 07/14/2011)
		* * *

08/05/2013	2870	Letter from James E. Cecchi to the Honorable Joel A. Pisano, U.S.D.J. re 2857 Application/Petition,. (Attachments: # 1 Exhibits A and B)(CECCHI, JAMES) (Entered: 08/05/2013)
		* * *
08/12/2013	2881	Letter from Karen A. Confoy re 2857 Application/Petition, 2870 Letter. (CONFOY, KAREN) (Entered: 08/12/2013)
		* * *
08/15/2013	2895	ORDER that the plaintiffs identified in Appendix A SHOW CAUSE why their pre-September 14, 2010 injury claims should not be dismissed and any briefs and supporting papers shall be filed within 45 days of entry of this Order; that Merck shall have 30 days to file a reply to plaintiffs' response to this Order; that plaintiffs' liaison counsel shall ensure all plaintiffs receive a copy of this Order. Signed by Judge Joel A. Pisano on 8/13/2013. (mmh) (Entered: 08/15/2013)
		* * *

09/30/2013	2946	DECLARATION of James E. Cecchi re 2895 Order to Show Cause, by PHYLLIS MOLNAR. (CECCHI, JAMES) (Entered: 09/30/2013)
		* * *
10/01/2013	2996	DECLARATION of Donald A. Ecklund re 2895 Order to Show Cause, by PHYLLIS MOLNAR. (Attachments: # 1 Exhibits to the Ecklund Declaration, # 2 Exhibits to the Ecklund Declaration, # 3 Exhibits to the Ecklund Declaration, # 4 Exhibits to the Ecklund Declaration, # 5 Exhibits to the Ecklund Declaration, # 6 Exhibits to the Ecklund Declaration, # 7 Exhibits to the Ecklund Declaration, # 8 Exhibits to the Ecklund Declaration, # 9 Exhibits to the Ecklund Declaration, # 10 Exhibits to the Ecklund Declaration, # 11 Exhibits to the Ecklund Declaration, # 12 Exhibits to the Ecklund Declaration, # 13 Exhibits to the Ecklund Declaration, # 14 Exhibits to the Ecklund Declaration, # 15 Exhibits to the Ecklund Declaration, # 16 Exhibits to the Ecklund

Declaration, # 17 Exhibits to the Ecklund Declaration, # 18 Exhibits to the Ecklund Declaration, # 19 Exhibits to the Ecklund Declaration, # 20 Exhibits to the Ecklund Declaration, # 21 Exhibits to the Ecklund Declaration, # 22 Exhibits to the Ecklund Declaration, # 23 Exhibits to the Ecklund Declaration, # 24 Exhibits to the Ecklund Declaration, # 25 Exhibits to the Ecklund Declaration, # 26 Exhibits to the Ecklund Declaration, # 27 Exhibits to the Ecklund Declaration, # 28 Exhibits to the Ecklund Declaration, # 29 Exhibits to the Ecklund Declaration, # 30 Exhibits to the Ecklund Declaration, # 31 Exhibits to the Ecklund Declaration, # 32 Exhibits to the Ecklund Declaration)(CECCHI, JAMES) (Entered: 10/01/2013)

* * *

10/30/2013 3035 DECLARATION of Karen A. Confoy in Support of Merck's Replies to Plaintiffs' Briefs in Response to Court's Order to Show Cause re 3032 Statement, 3031 Brief,,

		by MERCK SHARP & DOHME CORP.. (Attachments: # 1 Exhibits 2 & 3, # 2 Exhibit 4, 1 of 2, # 3 Exhibit 4, 2 of 2, # 4 Exhibits 5 & 6, # 5 Exhibit 7, 1 of 2, # 6 Exhibit 7, 2 of 2, # 7 Exhibit 8, 1 of 4, # 8 Exhibit 8, 2 of 4, # 9 Exhibit 8, 3 of 4, # 10 Exhibit 8, 4 of 4, # 11 Exhibits 9 - 11, # 12 Exhibits 13 - 17, # 13 Exhibits 19 & 20, # 14Exhibit 30, # 15 Exhibits 32 – 34, # 16 Exhibit 36, # 17 Exhibits 41 & 42, # 18 Exhibit 43, # 19 Exhibits 45 & 46, # 20 Exhibit 48, # 21 Exhibits 50 - 52, # 22 Exhibit 56, # 23 Exhibit 61, # 24 Exhibits 63 & 64, # 25 Exhibits 67 & 68, # 26 Exhibits 72 - 78, # 27 Exhibits 80 - 83)(CONFOY, KAREN) (Entered: 10/30/2013)
10/30/2013	3036	Exhibit to 3035 Declaration,,, by MERCK SHARP & DOHME CORP.. (Attachments: # 1 Exhibit 84, 2 of 3, # 2 Exhibit 84, 3 of 3, # 3 Exhibit 85, 1 of 7, # 4 Exhibit 85, 2 of 7, # 5 Exhibit 85, 3 of 7, # 6 Exhibit 85, 4 of 7,

		# 7 Exhibit 85, 5 of 7, # 8 Exhibit 85, 6 of 7, # 9 Exhibit 85, 7 of 7, # 10 Exhibits 86 - 88, # 11 Exhibit 89, 1 of 8, # 12 Exhibit 89, 2 of 8, # 13 Exhibit 89, 3 of 8, # 14 Exhibit 89, 4 of 8, # 15 Exhibit 89, 5 of 8, # 16 Exhibit 89, 6 of 8, # 17 Exhibit 89, 7 of 8, # 18 Exhibit 89, 8 of 8, # 19Exhibit 90, 1 of 8, # 20 Exhibit 90, 2 of 8, # 21 Exhibit 90, 3 of 8, # 22 Exhibit 90, 4 of 8, # 23 Exhibit 90, 5 of 8, # 24 Exhibit 90, 6 of 8, # 25 Exhibit 90, 7 of 8, # 26Exhibit 90, 8 of 8, # 27 Exhibits 91 - 93)(CONFOY, KAREN) (Entered: 10/30/2013)
10/30/2013	3037	Exhibit to 3035 Declaration,,, by MERCK SHARP & DOHME CORP.. (Attachments: # 1 Exhibit 12, # 2 Exhibit 18, # 3 Exhibits 21 - 29, # 4 Exhibit 31, # 5 Exhibit 35, # 6 Exhibits 37 - 40, # 7 Exhibit 44, # 8 Exhibit 47, 1 of 2, # 9 Exhibit 47, 2 of 2, # 10 Exhibit 49, # 11 Exhibits 53 - 55, # 12 Exhibits 57 & 58,

		# 13 Exhibit 59, 1 of 5, # 14 Exhibit 59, 2 of 5, # 15 Exhibit 59, 3 of 5, # 16 Exhibit 59, 4 of 5, # 17 Exhibit 59, 5 of 5, # 18 Exhibit 60, # 19 Exhibit 62, # 20 Exhibits 65 & 66, # 21 Exhibits 69 - 71, # 22 Exhibit 79)(CONFOY, KAREN) (Entered: 10/30/2013)
		* * *
10/02/2015	4065	Letter from Karen A. Confoy re 4056 Order on Motion to Seal. (Attachments: # 1 Exhibit A Documents (Part 1 of 18), # 2Exhibit A Documents (Part 2 of 18, # 3 Exhibit A Documents (Part 3 of 18, # 4 Exhibit A Documents (Part 4 of 18, # 5 Exhibit A Documents (Part 5 of 18, # 6 Exhibit A Documents (Part 6 of 18, # 7 Exhibit A Documents (Part 7 of 18, # 8 Exhibit A Documents (Part 8 of 18, # 9 Exhibit A Documents (Part 9 of 18, # 10 Exhibit A Documents (Part 10 of 18, # 11 Exhibit A Documents (Part 11 of 18, # 12 Exhibit A Documents (Part 12 of 18, # 13 Exhibit A Documents (Part 13 of 18, # 14 Exhibit A

Documents (Part 14 of 18, # 15 Exhibit A Documents (Part 15 of 18, # 16 Exhibit A Documents (Part 16 of 18, # 17 Exhibit A Documents (Part 17 of 18, # 18 Exhibit A Documents (Part 18 of 18, # 19 Exhibit B Documents (Part 1 of 5), # 20 Exhibit B Documents (Part 2 of 5), # 21 Exhibit B Documents (Part 3 of 5), # 22 Exhibit B Documents (Part 4 of 5), # 23 Exhibit B Documents (Part 5 of 5))(CONFOY, KAREN) (Entered: 10/02/2015)

* * *

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (No. II) *This Document Relates To All Cases*	MDL No. 2243 Civ. No. 08-08 (GEB) (LHG)

~~{PROPOSED}~~ CASE MANAGEMENT ORDER NO. 4
(Pretrial Schedule)

It appearing that the civil actions listed on Schedule A, attached hereto, which were transferred to this Court by order of the Judicial Panel on Multidistrict Litigation pursuant to its order of May 23, 2011, merit special attention as complex litigation, it is therefore ORDERED that:

1. APPLICABILITY OF ORDER

The provisions of this Order shall govern the practice and procedure in actions: (1) transferred to this Court by the Judicial Panel on Multidistrict Litigation pursuant to its order of May 23, 2011 listed on Schedule A; (2) all related actions alleging that the prescription medicine FOSAMAX® and/or alendronate sodium caused patients prescribed it to suffer femur fractures or similar bone injuries that were filed in the District of New Jersey and were previously before this Court; and (3) any "tag-along" actions later filed in, removed to, or transferred to this Court. The Clerk will send a copy of this Order to

counsel for any plaintiffs or newly named defendants in any case newly filed in or transferred to this Court. Moreover, all pending motions and outstanding discovery requests in the transferor courts are vacated and superseded by this Order and subsequent orders issued by this Court.

The civil actions listed on Schedule A are coordinated for pretrial purposes. Any "tag-

* * *

8. REMAND STIPULATIONS

In the event that a case is remanded to the transferor court, the parties shall furnish to the Clerk of the transferee court a stipulation or designation of the contents of the record and furnish all necessary copies of any pleadings filed so as to enable the Clerk of the transferee court to comply with the order of remand.

9. EARLY DISCOVERY AND TRIAL CASES

9.1 Selection of Early Discovery Cases

All cases in which Merck is the only defendant that have been filed in, transferred to, or subject to transfer to this Court by September 14, 2011 are available for selection. Plaintiffs' counsel will make their best efforts to file any additional cases of which they are presently aware that will be part of this MDL by September 14, 2011. The parties will meet and confer regarding a process for the selection of 40 cases, a list of which shall be filed with the Court by September 23, 2011. Should the parties be unable to reach agreement on a process for selecting the 40 cases, the parties are to submit their respective proposals to the Court by August 22, 2011. In addition, the parties

shall further meet and confer to address *Lexecon*-related issues with respect to the 40 cases selected for early discovery; should the parties be unable to agree with respect to the issue, the parties shall submit their respective proposals to the Court by August 22, 2011. Fact discovery in these 40 cases will be completed by July 31, 2012.

9.2 Process for Selection of Trial Candidates

The Court intends to try bellwether cases in this litigation. The parties are to meet and confer on a process for selection of three or four cases for early trial ("Early Trial Cases") from those cases identified pursuant to Section 9.1 above; the trial case selection process used by the parties shall be structured such that the Early Trial Cases are identified by April 30, 2012.

9.3 Expert and Pre-Trial Motions

A. Expert Discovery Expert discovery on general causation (i.e., whether Fosamax or alendronate can be a cause of femur fractures), as well as all expert discovery in the Early Trial Cases, should be completed by ~~December 14~~ **November 28**, 2012, in accordance with the following schedule:

~~September 10~~ **August 31**, 2012 – Plaintiffs' Rule 26(a)(2) disclosures shall be served.

~~October 15~~ **October**, 2012 – Merck's Rule 26(a)(2) disclosures shall be served.

~~November 12~~ **October 26**, 2012 – Depositions of Plaintiffs' experts shall be completed.

~~December 14~~ **November 28**, 2012 – Depositions of Merck's experts shall be completed.

B. *Daubert* Motions

Any *Daubert* motions on general causation or in the Early Trial Cases shall be filed by ~~January 4, 2013~~ **December 3, 2012**. Opposition briefs shall be filed by January ~~30~~, 2013, and reply briefs shall be filed by ~~February 13~~ **January 17**, 2013. A *Daubert* hearing ~~will be held in February 2013~~ **may be scheduled at the Court's discretion.**

C. Dispositive Motions in the Early Trial Cases

Dispositive motions in the Early Trial Cases shall be filed on ~~January 4, 2013~~ **December 3, 2012**. Opposition briefs shall be filed by January ~~30~~, 2013, and any reply briefs shall be filed by ~~February 13~~ **January 17**, 2013. Oral argument on any dispositive motions filed in the Early Trial Case with the earliest trial date ~~will be held in February 2013~~ **may be scheduled at the Court's discretion**. A separate schedule will be issued for ~~oral argument on any dispositive motions filed in the remaining Early Trial Cases, as well as for~~ the timing of motions in limine to be filed in each of the Early Trial Cases.

9.4 Trial

The first trial shall begin on the first available date after March 1, 2013. While it is premature to make predictions regarding the anticipated length of trials, the parties have informed the Court that the four bellwether trials in the Fosamax ONJ MDL have each lasted approximately 3 weeks.

Next scheduling and case management conference September 21, 2011 @ 1pm in Trenton.

SO ORDERED.

Dated: Trenton New Jersey
July 14, 2011

/s/ Garrett E. Brown, JR.
GARRETT E. BROWN, JR.
UNITED STATES DISTRICT JUDGE

Attachments

ANAPOL, SCHWARTZ, WEISS, COHAN FELDMAN & SMALLEY, P.C.
BY: TRACY A. FINKEN, ESQUIRE
GREGORY S. SPIZER, ESQUIRE
AMBER RACINE, ESQUIRE
1040 KINGS HIGHWAY NORTH
CHERRY HILL, NJ 08034
(856) 482-1600; FAX (856) 482-1911

ATTORNEY FOR PLAINTIFFS

IN THE UNITED STATES DISTRICT COURT OF NEW JERSEY

SUSAN STEVES and	:	**CIVIL ACTION**
JAMES STEVES, wife/husband	:	**NO.**
10111 State Highway 37	:	
Ogdensburg, NY 13669,	:	
Plaintiffs	:	
	:	
vs.	:	
MERCK SHARPE & DOHME	:	**JURY TRIAL**
One Merck Drive	:	**DEMANDED**
White House Station, NJ, 08889	:	
	:	
TEVA PHARMACEUTICALS	:	
USA, INC.	:	
1090 Horsham Road	:	
North Wales, PA	:	
	:	
NORTHSTAR RX, LLC	:	
PHARMACEUTICALS, INC.	:	
4971 Southridge Blvd. Suite 101	:	
Memphis, TN 38141	:	
	:	
SANOFI-AVENTIS, U.S., INC	:	
55 Corporate Drive	:	
Bridgewater, New Jersey 08807	:	
	:	
SANOFI-AVENTIS, U.S., LLC	:	
55 Corporate Drive	:	
Bridgewater, New Jersey 08807	:	

and	:
WARNER CHILCOTT (US), LLC	:
100 Enterprise Drive	:
Rockaway, New Jersey 07866	:
	:
Defendants	:
	:

COMPLAINT

Plaintiffs, Susan Steves and James Steves, wife and husband, by way of Complaint against Defendants, Merck Sharpe & Dohme Corporation, f/k/a Merck & Co., Inc. ("Merck"), TEVA Pharmaceutical USA, Inc., ("TEVA"), NorthStar Pharmaceuticals, Inc. ("NorthStar") (Merck, TEVA and NorthStar referred to collectively as "Fosamax Defendants"); Sanofi-Aventis U.S. Inc., Sanofi-Aventis U.S. LLC, and Warner Chilcott (US), LLC, As Successor to Procter & Gamble Pharmaceuticals, Inc. (collectively referred to herein as "Actonel Defendants"), upon information and belief, allege as follows:

PARTIES

1. Plaintiffs, Susan Steves and James Steves, are wife and husband and are citizens of the State of New York, residing at 10111 State Highway 37, Ogdensburg, New York, 13669.

2. Defendant, Merck Sharpe & Dohme, f/k/a Merck & Co., Inc. (hereinafter "Merck"), is a corporation organized and existing under the laws of the State of New Jersey, with its principal place of business at One Merck Drive, White House Station, NJ, 08889.

* * *

62. Defendants knew of the significant risk of severely suppressed bone turnover, brittle bones, multiple stress fractures and low energy femoral fractures that could result from long-term bisphosphonate use, but Defendants did not adequately and sufficiently warn or instruct consumers, including Plaintiff Susan Steves, her physician or the medical community, of such risks.

63. As a direct result, Plaintiff, Susan Steves, was prescribed ACTONEL for approximately six (6) years and FOSAMAX/ALENDRONATE SODIUM for approximately seven (7) years and has been permanently and severely injured, having suffered serious consequences from long-term FOSAMAX use. Plaintiff, Susan Steves, requires and will in the future require ongoing medical care and treatment.

64. Plaintiff, Susan Steves, has suffered from mental anguish from the knowledge that she will have life-long complications as a result of the injuries she sustained from the use of FOSAMAX/ALENDRONATE SODIUM and ACTONEL.

65. Plaintiff, Susan Steves, was prescribed and began taking ACTONEL in approximately 1998.

66. Plaintiff, Susan Steves, was prescribed and began taking brand name FOSAMAX in approximately September 2004.

67. Plaintiff, Susan Steves, began to use ALENDRONATE SODIUM, generic FOSAMAX, manufactured by Defendant, TEVA, in approximately May 2008.

68. Plaintiff, Susan Steves, began to use ALENDRONATE SODIUM, generic FOSAMAX,

manufactured by Defendant, NorthStar, in approximately September 2010.

69. Plaintiff, Susan Steves, used ACTONEL as prescribed and in a foreseeable manner consistently from approximately 1998 through approximately 2004.

70. Plaintiff, Susan Steves, used FOSAMAX as prescribed and in a foreseeable manner consistently from approximately 2004 through approximately May 2008.

71. Plaintiff, Susan Steves, used generic ALENDRONATE SODIUM, manufactured by Defendant, TEVA, as prescribed and in a foreseeable manner consistently from approximately May 2008 through approximately September 2009.

72. Plaintiff, Susan Steves, used generic ALENDRONATE SODIUM, manufactured by Defendant, NorthStar, as prescribed and in a foreseeable manner consistently from approximately September 2009 through approximately July 2011.

73. As a direct and proximate result of her long-term FOSAMAX/ALENDRONATE SODIUM and ACTONEL use, Plaintiff, Susan Steves, suffered severely suppressed bone turnover and severe femur fractures.

74. Plaintiff, Susan Steves, used FOSAMAX, as prescribed and in a foreseeable manner consistently in brand-name form from approximately 2004 though May 2008 and, subsequently, in generic form, known as ALENDRONATE SODIUM, from approximately May 2008 through June 2011

75. As a direct and proximate result of her long-term FOSAMAX/ALENDRONATE SODIUM use, Plaintiff, Susan Steves, suffered severely suppressed bone turnover and femur fractures.

76. On or about March 25, 2008, Plaintiff suffered a severe femur fracture of her left leg.

77. On or about July 16, 2011, Plaintiff suffered a severe femur fracture of her right leg.

78. It is believed and therefore averred that Susan Steves' low energy femur fractures were suffered due to the harmful long-term effects of FOSAMAX/ALENDRONATE SODIUM and ACTONEL use, a consequence that was never made known to Plaintiff, Susan Steves, or her physicians by Defendants.

79. Plaintiff, Susan Steves, as a direct and proximate result of long-term FOSAMAX/ALENDRONATE SODIUM and ACTONEL use, suffered severe mental and physical pain and suffering and has sustained permanent injuries and emotional distress.

80. Plaintiff, Susan Steves, used ACTONEL which had been provided to her in a condition that was substantially the same as the condition in which it was manufactured and sold.

81. Plaintiff, Susan Steves, used FOSAMAX/ALENDRONATE SODIUM which had been provided to her in a condition that was substantially the same as the condition in which it was manufactured and sold.

82. Plaintiff, Susan Steves, would not have used ACTONEL for so many years had Defendants properly disclosed the risks associated with its long-term use.

83. Plaintiff, Susan Steves, would not have used FOSAMAX/ALENDRONATE SODIUM for so many years had Defendants properly disclosed the risks associated with its long- term use.

84. Defendants, through their affirmative misrepresentations and omissions, actively concealed from Plaintiff, Susan Steves, and her physicians the true and significant risks associated with long-term FOSAMAX/ALENDRONATE SODIUM and ACTONEL use. The running of any applicable statute of limitations has been tolled by reason of Defendants' fraudulent concealment.

85. As a result of Defendants' actions, Plaintiff, Susan Steves, and her prescribing physicians were unaware, and could not have reasonably known or have learned through reasonable diligence, that Plaintiff had been exposed to the risks identified in this complaint, and that those risks were the direct and proximate result of Defendants' acts, omissions, and misrepresentations.

86. It is believed and therefore averred that Defendants knew or should have known and failed to warn that long term use of FOSAMAX/ALENDRONATE SODIUM and ACTONEL was unsafe because it could cause low energy femur fractures of the type that plaintiff, Susan Steves, suffered.

87. Defendants with their heightened knowledge and experience, knew or should have known that long term use of bisphosphonates, including

FOSAMAX/ALENDRONATE SODIUM and ACTONEL, could inhibit the production of new bone cells (osteoblasts) and therefore would prevent repair of naturally occurring micro fractures in the femur which could lead to serious low energy femur fractures, and/or that prolonged suppression of bone remodeling with FOSAMAX/ALENDRONATE SODIUM could lead to serious low energy femur fractures; and that femur fractures caused by long term FOSAMAX/ALENDRONATE SODIUM use could occur despite the apparent absence of sufficient trauma.

88. While FOSAMAX/ALENDRONATE SODIUM has been marketed, it is believed and therefore averred, that prior to plaintiff's suffering femur fractures, Defendants received adverse reaction reports from different FOSAMAX/ALENDRONATE SODIUM users throughout the country that these patients were experiencing bone brittleness, susceptibility to fractures, femoral stress fractures, and/or low energy femoral shaft fractures after long-term use of FOSAMAX/ALENDRONATE SODIUM.

89. While ACTONEL has been marketed, it is believed and therefore averred, that prior to plaintiff's suffering femur fractures, Defendants received adverse reaction reports from different ACTONEL users throughout the country that these patients were experiencing bone brittleness, susceptibility to fractures, femoral stress fractures, and/or low energy femoral shaft fractures after long-term use of ACTONEL.

90. It is believed and therefore averred that Defendants disregarded and has refused to follow up

on the reports of patients, who after using FOSAMAX/ALENDRONATE SODIUM and ACTONEL, have experienced and reported bone brittleness, susceptibility to fractures, femoral stress fractures, and/or low energy femoral shaft fractures.

91. It is believed and therefore averred that Defendants failed to submit these reported adverse consequences to the FDA and has failed to advise physicians and the public.

* * *

COUNT III

PRODUCTS LIABILITY-FAILURE TO WARN (N.J. Products Liability Act-N.J.S.A. 2A58C-1) AS TO FOSAMAX DEFENDANTS

119. Plaintiffs repeat and incorporate by reference all other paragraphs of this Complaint as if fully set forth herein.

120. Defendant Merck researched, developed, designed, tested, manufactured, inspected, labeled, distributed, marketed, promoted, sold, and otherwise released into the stream of commerce the pharmaceutical, FOSAMAX, and in the course of same, directly advertised or marketed the product to consumers or persons responsible for consumers, and therefore had a duty to warn of the risks associated with the use of FOSAMAX.

121. Defendant, NorthStar, manufactured, inspected, labeled, distributed, marketed, promoted, sold, and otherwise released into the stream of commerce the pharmaceutical, ALENDRONATE SODIUM, and in the course of same, directly

advertised or marketed the product to consumers or persons responsible for consumers, and therefore had a duty to warn of the risks associated with the use of ALENDRONATE SODIUM.

122. Defendant TEVA manufactured, inspected, labeled, distributed, marketed, promoted, sold, and otherwise released into the stream of commerce the pharmaceutical, ALENDRONATE SODIUM, and in the course of same, directly advertised or marketed the product to consumers or persons responsible for consumers, and therefore had a duty to warn of the risks associated with the use of ALENDRONATE SODIUM.

123. FOSAMAX/ALENDRONATE SODIUM was under the exclusive control of Defendants and was unaccompanied by appropriate warnings regarding the risk of severely suppressed bone turnover, resulting stress fractures, femur fractures and other severe and permanent injuries associated with its use. The warnings given did not accurately reflect the risk, incidence, symptoms, scope or severity of such injuries to the consumer. The promotional activities of Defendants further diluted or minimized the warnings given with the product.

124. Defendants downplayed the serious and dangerous side effects of FOSAMAX/ALENDRONATE SODIUM to encourage sales of the product; consequently, Defendants placed its profits above its customers' safety.

125. FOSAMAX/ALENDRONATE SODIUM was defective and unreasonably dangerous when it left the possession of the Defendants in that they contained warnings insufficient to alert Plaintiff, Susan Steves,

to the dangerous risks and reactions associated with them, including, but not limited to severely suppressed bone turnover and femur fractures. Even though Defendants knew or should have known of the risks and reactions associated with FOSAMAX/ALENDRONATE SODIUM, they still failed to provide warnings that accurately reflected the signs, symptoms, incident, scope, or severity of the risks associated with the product.

126. Plaintiff, Susan Steves, used FOSAMAX/ALENDRONATE SODIUM as intended or in a reasonably foreseeable manner.

127. Plaintiff, Susan Steves, could not have discovered any defect in FOSAMAX/ALENDRONATE SODIUM through the exercise of reasonable care.

128. Fosamax Defendants, as manufacturers of pharmaceutical drugs, are held to the level of knowledge of an expert in the field and, further, Defendants had knowledge of the dangerous risks and side effects of FOSAMAX/ALENDRONATE SODIUM.

129. Plaintiff, Susan Steves, did not have the same knowledge as Defendants and no adequate warning was communicated to her physicians.

130. Defendants had a continuing duty to warn consumers, including Plaintiff and her physicians, and the medical community of the dangers associated with FOSAMAX/ALENDRONATE SODIUM, and by negligently and/or wantonly failing to adequately warn of the dangers associated with its use, Defendants breached their duty.

131. Although Defendants knew, or were reckless in not knowing, of the defective nature of FOSAMAX/ALENDRONATE SODIUM, they

continued to design, manufacture, market, and sell FOSAMAX/ALENDRONATE SODIUM without providing adequate warnings and instructions concerning the use of FOSAMAX/ALENDRONATE SODIUM so as to maximize sales and profits at the expense of the public health and safety, in knowing, conscious, and deliberate disregard of the foreseeable harm caused by FOSAMAX/ALENDRONATE SODIUM.

132. As a direct and proximate result of Defendants' failure to adequately warn or other acts and omissions of Defendants described herein, Plaintiff, Susan Steves, developed severely suppressed bone turnover, causing her to suffer severe and permanent injuries, including severe femur fractures, pain and mental anguish, including diminished enjoyment of life, and fear of developing other harmful conditions.

133. In addition, Defendants' conduct in the packaging, warning, marketing, advertising, promotion, distribution, and sale of FOSAMAX/ALENDRONATE SODIUM was committed with knowing, conscious, willful, wanton, and deliberate disregard for the value of human life, and the rights and safety of consumers such as Plaintiff, Susan Steves, thereby entitling Plaintiff to punitive damages so as to punish Defendants and deter it from similar conduct in the future.

WHEREFORE, Plaintiffs demand judgment against Fosamax Defendants for any and all damages, (including, but not limited to severe physical pain and suffering; mental anguish; severe anxiety; loss of life's pleasures; loss of enjoyment of life; and loss of future earning capacity, future earnings and income), as well

as punitive damages, cognizable in accordance with the laws of the State of New Jersey, together with interest, cost of suit and counsel fees.

* * *

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: FOSOMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (No. II) *This Document Relates to: Carol Knopick v. Merck & Co. and Merck Sharpe & Dohme Corp.*	Docket No. MDL Docket No. 2243 Civ. No. 08-08(GEB) (LHG) **COMPLAINT AND DEMAND FOR JURY TRIAL** **JUDGE JOEL A. PISANO**

COMPLAINT

1. This is an action for personal injury, statutory, compensatory, and punitive damages due to Plaintiff as a result of Defendants' concealment of risks associated with their drug Fosamax as well as their gross exaggeration of the purported fracture reduction benefits conferred by the drug Fosamax, and their over promotion of the drug for non-approved, or "off- label" indications.

PARTIES

2. Plaintiff Carol Knopick ("Plaintiff") currently resides at 8511 Barstow, Lenexa, Kansas 66219. Plaintiff used the medication Fosamax for the

treatment and/or prevention of osteopenia and/or osteoporosis.

3. Defendant Merck & Co., Inc. ("Merck & Co.") is a corporation organized and existing under the laws of the State of New Jersey, with its principal place of business located at One Merck Drive, Whitehouse Station, New Jersey. Merck & Co., a global pharmaceutical company, directly and through its agents, advertises, solicits, promotes, and distributes prescription drugs, including Fosamax.

4. Defendant Merck Sharpe & Dohme Corp. is a subsidiary of Merck & Co. and is a corporation incorporated under the laws of the State of New Jersey with its principal place of business located at One Merck Drive, Whitehouse Station, New Jersey.

5. At all times relevant to this Complaint, (collectively, "Defendants") designed, manufactured, marketed, distributed, and sold for profit the prescription drug product known as Fosamax through interstate commerce, including in New Jersey.

* * *

B. Fosamax Causes Femur Fractures and Other Serious Injuries

30. Over the last few years, there have been an increasing number of reports of patients suffering multiple fractures and low energy femoral fractures as a result of severely suppressed bone turnover caused by Fosamax use. Severely suppressed bone turnover from Fosamax use has been well recognized in the medical literature.

31. There is also evidence from at least one animal study that the severe suppression of bone turnover

and bone remodeling that occurs with alendronate therapy, can result in the accumulation of microdamage in bone as well as a reduction in some of the biomechanical properties of bone. Mashiba et al., *Suppressed Bone Turnover by Biphosphonates Increases Microdamage Accumulation and Reduces Some Biomechanical Properties in Dog Rib*, 15J, Bone and Mineral 613 (2000). These findings were further reflected in human studies: "Our findings raise the possibility that severe suppression of bone turnover may develop during long-term alendronate therapy, resulting in increased susceptibility to, and delayed healing of, nonspinal fractures." Odvina, Clarita V., et al., *Severely Suppressed Bone Turnover: A Potential Complication of Alendronate Therapy*, 90 J. Clin. Endocrinal. Metab. 1294–1301 (2005).

32. On January 7, 2008, the FDA issued a medical advisory warning doctors and Fosamax patients of the "possibility of severe and sometimes incapacitating bone, joint, and/or muscle pain," and advising physicians to discontinue prescribing Fosamax if such complaints occurred during therapy. One week later, the January 15, 2008 issue of the Journal of Rheumatology contained an article that concluded that Fosamax patients have a 287% higher chance of developing osteonecrosis (of the jaw, hip, and knee) than those not taking the drug.

33. On February 23, 2011, the journal of the American Medical Association contained an article entitled *Bisphosphonate Use and the Risk of Subtrochanteric or Femoral Shaft Fractures in Older Women*. The study concluded that "bisphosphonate use, treatment for 5 years or longer was associated with an increased risk of subtrochanteric or femoral

shaft fracture (adjusted odds ratio 2.74; 95% confidence interval, 1.25–6.02)."

C. Defendants' Failure to Warn of the Dangers of Fosamax

34. Despite its knowledge of this dangerous side effect that can result from Fosamax use, Defendants refuse to warn patients, physicians and the medical community about the risk of severely suppressed bone turnover. Defendants continue to defend Fosamax, mislead physicians and the public, and minimize unfavorable findings.

35. Defendants failed to change any of their prescribing information, package inserts or drug manuals supplied to the medical and pharmaceutical professions and the general public in order to warn of the potential for femur fractures after long-tern Fosamax use, until finally ordered to do so by the FDA on October 13, 2010.

36. Consumers, including Plaintiff, who have used Fosamax for treatment of osteoporosis/osteopenia, have several alternative available safer products to treat the conditions but have not been adequately warned about the significant risks and lack of benefits associated with Fosamax therapy.

37. Defendants knew of the significant risk of severely suppressed bone turnover, brittle bones, multiple fractures and low energy femoral fractures that could result from Fosamax use, but did not adequately and sufficiently warn consumers, including Plaintiff, «Phisher» physicians or the medical community, of such risks.

D. Plaintiff's Use of Fosamax

38. Plaintiff was prescribed and began taking Fosamax in approximately 2003 through 2008. Fosamax was provided to Plaintiff in a condition that was substantially the same as the condition in which it was manufactured and sold.

39. Plaintiff used Fosamax as prescribed and in a foreseeable manner.

40. After 2008, Plaintiff was prescribed and took a generic bisphosphonate medication from approximately 2008 through 2010.

41. As a direct and proximate result of her Fosamax use, Plaintiff suffered from stress fractures of her right and left femurs, which was diagnosed on approximately May 9, 2009. Plaintiff also suffered from a severe fracture of her right femur, which was diagnosed on approximately September 2, 2010.

42. Plaintiff, as a direct and proximate result of Fosamax use, suffered severe mental and physical pain and suffering and has sustained permanent injuries and emotional distress.

43. Plaintiff would not have used and her physicians would never have been prescribed Fosamax for so many years had Defendants properly disclosed the risks associated with its use.

* * *

COUNT II

PRODUCTS LIABILITY – FAILURE TO WARN

(N.J. Products Liability Act – N.J.S.A. 2A:58C-2 *et seq.*)

55. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

56. Defendants researched, developed, designed, tested, manufactured, inspected, labeled, distributed, marketed, promoted, sold, and otherwise released into the stream of commerce Fosamax, and directly advertised or marketed the product to consumers or persons responsible for consumers, and therefore had a duty to warn of the risks associated with the use of Fosamax.

57. Fosamax was under the exclusive control of Defendants and was unaccompanied by appropriate warnings regarding the risk of severely suppressed bone turnover, resulting fractures, or low energy femoral fractures and other severe and permanent injuries associated with its use. The warnings given did not accurately reflect the risk, incidence, symptoms, scope or severity of such injuries to the consumer or physicians. The promotional activities of Defendants further diluted or minimized the warnings given with the product.

58. Defendants downplayed the serious and dangerous side effects of Fosamax to encourage sales of the product; consequently, Defendants placed their profits above its consumers' safety.

59. Fosamax was defective and unreasonably dangerous when it left the possession of Defendants in

that it contained warnings insufficient to alert Plaintiff to the dangerous risks and reactions associated with it, including, but limited to severely suppressed bone turnover, multiple fractures, and low energy femoral fractures. Even though Defendants knew or should have known of the risks and reactions associated with Fosamax, it still failed to provide warnings that accurately reflected the signs, symptoms, incident, scope, or severity of the risks associated with the product.

60. Plaintiff used Fosamax as intended or in a reasonably foreseeable manner.

61. Plaintiff could not have discovered any defect in Fosamax through the exercise of reasonable care.

62. Defendants, as manufacturers of pharmaceutical drugs, are held to the level of knowledge of an expert in the field and, further, had knowledge of the dangerous risks and side effects of Fosamax.

63. Plaintiff did not have the same knowledge as Defendants and no adequate warning was communicated to her physicians.

64. Defendants had a continuing duty to warn consumers, including Plaintiff and «Phisher» physicians, and the medical community of the dangers associated with Fosamax, and by negligently and/or wantonly failing to adequately warn of the dangers associated with its use, Defendants breached their duty.

65. Although Defendants knew, or were reckless in not knowing, of the defective nature of Fosamax, they continued to design, manufacture, market, and sell Fosamax without providing adequate warnings and

instructions concerning the use of Fosamax so as to maximize sales and profits at the expense of the public health and safety, in knowing, conscious, and deliberate disregard of the foreseeable harm caused by Fosamax.

66. As a direct and proximate consequence of Defendants' actions, omissions, and misrepresentations, Plaintiff suffered severely suppressed bone turnover, bilateral stress fractures and a severe fracture of her right femur. In addition, Plaintiff required and will continue to require healthcare and services and Plaintiff has incurred and will continue to incur medical and related expenses as a result of her injuries. Plaintiff also has suffered and will continue to suffer mental and physical pain and suffering, diminished capacity for the enjoyment of life, a diminished quality of life, increased risk of premature death, aggravation of preexisting conditions and activation of latent conditions, and other losses and damages.

67. In addition, Defendants' conduct in the packaging, warning, marketing, advertising, promotion, distribution, and sale of Fosamax was committed with knowing, conscious, willful, wanton, and deliberate disregard for the value of human life, and the rights and safety of consumers such as Plaintiff, thereby entitling Plaintiff to punitive damages so as to punish Defendants and deter them from similar conduct in the future.

WHEREFORE, Plaintiff demands judgment against Defendants individually, jointly and/or severally and demands compensatory, statutory and punitive damages available under New Jersey law, together

with interest, costs of suit, attorneys' fees and all such other relief as the Court deems just and proper.

* * *

1. Did Bernadette Glynn prove by the preponderance of the evidence that she experienced an atypical femur fracture in April 2008?

   YES _____ NO ____X____

   (If you answered "NO" to Question #1, please skip to the end, date and sign the verdict form, and inform the court officer that you have reached a verdict. If you answered "YES" to Question #1, please proceed to Question #2.)

2. Did Bernadette Glynn prove by the preponderance of the evidence that her use of Fosamax was a substantial contributing factor to her atypical femur fracture?

   YES _____ NO _____

   (If you answered "NO" to Question #2, please skip to the end, date and sign the verdict form, and inform the court officer that you have reached a verdict. If you answered "YES" to Question #2, please proceed to Question #3.)

3. Did Bernadette Glynn prove by the preponderance of the evidence that Merck should have warned her Fosamax prescribers of a risk of atypical femur fracture prior to her injury and that Ms. Glynn's prescribers would not have prescribed Fosamax to her had they been warned about atypical femur fracture?

   YES _____ NO _____

(If you answered "NO" to Question #3, please skip to the end, date and sign the verdict form, and inform the court officer that you have reached a verdict. If you answered "YES" to Question #3, please proceed to Question #4.)

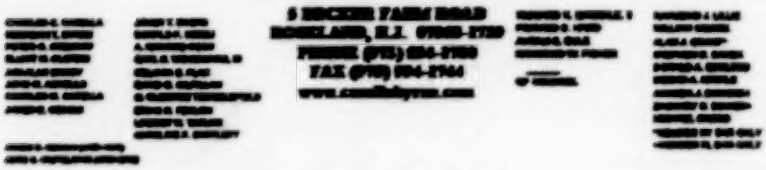
4. What amount, if any, will fairly and adequately compensate Plaintiff for her pain and suffering related to her injury?

$_____

DATED: TRENTON, NEW JERSEY
APRIL 29, 2013

CARELLA, BYRNE, CECCHI, OLSTEIN, BRODY & AGNELLO, P.C.

COUNSELLORS AT LAW



August 5, 2013

Via ECF

Hon. Joel A. Pisano
United States District Judge
Clarkson S. Fisher Bldg.
& U.S. Courthouse
402 E. State Street
Trenton, New Jersey 08608

Re: *In re: Fosamax (Alendronate Sodium) Products Liability Litigation*
Master Docket 3:08-08 (JAP)(LHG)

Dear Judge Pisano:

This firm, together with Seeger Weiss LLP, is co-liaison counsel for the plaintiffs in the above-referenced matter. Please accept this letter brief in lieu of a more formal opposition to defendant Merck Sharp & Dohme Corp.'s ("Merck") application for the entry of a show-cause order. (Dkt. No. 2857) Plaintiffs respectfully request that the Court deny Merck's application.

A. Merck's Request for Entry of an Order to Show Cause is Procedurally Improper and Must be Denied.

Plaintiffs oppose the entry of Merck's proposed order because it is an inappropriate procedural mechanism for the adjudication of Plaintiffs' claims. Merck selected this mechanism without any guidance from the Court that Plaintiffs are aware of. Prior to filing, Merck engaged in no pre-motion conference or meet and confer with the Plaintiffs to discuss appropriate scheduling, or whether an order to show cause would be the appropriate means for seeking dismissal in this case. Merck has provided no indication why the use of an order to show cause, as opposed to a standard notice of motion, is warranted here. Clearly, Merck took this posture to avoid the requirements of a Rule 56 Motion for Summary Judgment, which would require Merck to set forth the facts and evidence on which it relied in seeking to preempt the claims of all Plaintiffs subject to the proposed order.

Issuing Merck's proposed order to show cause would be highly prejudicial to Plaintiffs, especially considering that the order concerns a case dispositive issue, such a procedure was never discussed by the Court or Merck in the presence of the Plaintiffs, and the preposterous 30-day timeframe Merck wishes to impose on hundreds of separate Plaintiffs.

At the July 18, 2013 status conference held to discuss how to address the preemption issue in this litigation after the *Glynn* preemption ruling, there was no mention of Merck requesting an order to show cause. Ex. A, Transcript of July 18, 2013 Status

Conference ("Status Conference"). Rather, at the July 18, 2013 conference, the Court indicated that if Plaintiffs did not file a notice of appeal in the *Glynn* case, Merck would be required to file a motion to dismiss all of the pre-label change cases on the basis of preemption. *Id.* at 14:13–15.

An order to show cause is not an appropriate means to resolve the preemption issue in this litigation. As noted in Charles Wright and Arthur R. Miller's treatise on federal procedure, orders to show cause are not provided for in the Federal Rules of Civil Procedure, and parties' use of notices of motions is preferable. Orders to Show Cause and Rules Nisi, 5 Fed. Prac. & Proc. Civ. § 1195 (3d ed.). Generally, such orders are invoked when there is some compelling issue that requires expedited resolution to prevent an imminent harm. The Local Civil and Criminal Rules of the District of New Jersey ("Local Rules") only mention use of orders to show cause in the context of preliminary injunctions, disciplinary proceedings, and arbitration. Local Rules 65.1, 104.1, 201.1. The Local Rules do not contemplate the use of an order to show cause outside of these contexts. And even within the context of issuing a preliminary injunction, the Local Rules specify that:

> No order to show cause to bring on a matter for hearing will be granted except on a clear and specific showing by affidavit or verified pleading of good and sufficient reasons why a procedure other than by notice of motion is necessary.

Local Civil Rule 65.1(a). Without even an attempt to justify the basis for the order to show cause, the Court should deny Merck's request for relief.

B. Entry of Merck's Proposed Order Would Eviscerate Plaintiffs' Due Process Entitlement to be Heard on the Preemption Issue.

Entry of Merck's proposed order to show cause would constitute an egregious violation of due process and accepted standards for the management of complex litigation. The Due Process Clause requires that everyone shall have the protection of their day in court, which "hears before it condemns and proceeds not arbitrarily, but upon inquiry, and renders judgment only [after a full and fair presentation of the evidence] after trial." *Truax v. Corrigan*, 257 U.S. 312, 332 (1921). While aggregation of cases does not per se violate the requirements of due process, any form of aggregation must honor a party's right to due process so as not to run afoul of the U.S. Constitution. Thus, at a minimum, the judicial process must provide a meaningful opportunity for all parties to be heard.

Were the Court to adopt Merck's request to aggregate and dispose of Plaintiffs' suits in the inappropriate manner proposed, the Court would deprive Plaintiffs of their fundamental right to be heard. Following the *Glynn* trial, the Court informed the parties that it would not apply its forthcoming preemption decision in *Glynn* to the remaining Fosamax femur cases pending in the federal litigation. The Court stated on the record that "[t]he point is I'm not going to enter any order which terminates 3300 cases in an MDL. I'm going to enter an order that does or does not terminate Mrs. Glynn's case." Ex. B, Transcript of April 30, 2013 Post-Trial Status Conference, at 25:17-20. The Court further noted that if evidence bearing on preemption was proffered in the

next trial case, *Zessin v. Merck*, the Court would consider such evidence at that time. *Id.* at 20:10-11. Though the time to disclose experts in Zessin had closed, that is not so for any of the other cases in the MDL.

Plaintiffs strongly urge the Court to reconsider its position that the *Glynn* trial record may be used to adjudicate preemption in other cases. As counsel for Plaintiffs informed the Court at the July 18 Status Conference, experts have yet to be designated in any case aside from *Glynn* and *Zessin*, and Merck has turned over many documents to Plaintiffs after it was too late to review them and incorporate them into the *Glynn* trial. Ex. A, Status Conf. Tr. 8:9-9:16; 10:21-11:5. Merck proposes that the unfavorable evidentiary rulings from the *Glynn* trial record, which excluded much of the relevant preemption evidence, be applied to their claims. Merck's attempt to substitute the *Glynn* record, in place of Plaintiffs' constitutionally-entitled day in court, is patently unjust and violates their fundamental rights.

The Court should not allow Merck to fast-track an omnibus decision on a case dispositive issue that concerns the rights of hundreds of injured Plaintiffs. The preemption issue is not ripe for determination on a global basis in the manner proposed. MDL Plaintiffs have not been afforded the opportunity to submit expert reports different from those disclosed in *Glynn*. Merck seeks to deprive hundreds of Plaintiffs from coming forward with their own experts on what was known, knowable, and appropriate to warn of at the different points in time. These hundreds of litigants have not been afforded an evidentiary hearing where they could make their preemption case, present

evidence, and cross-examine Merck's regulatory expert's testimony on the labeling issues. Plaintiffs should be afforded a hearing on preemption that enables them to create a full record, which would incorporate pertinent expert testimony and all relevant materials obtained in discovery, including those provided by Merck during and after the *Glynn* trial.

Plaintiffs also object to the entry of Merck's proposed order because, though preemption is decided as a matter of law by the court, underlying factual issues concerning the state of scientific knowledge over time and the likely regulatory response at distinct points prevent the Court from adjudicating hundreds of Plaintiffs' cases under a single preemption analysis. As the Supreme Court aptly explained, "*consolidation is permitted as a matter of convenience and economy in administration, but does not merge the suits into a single cause, or change the rights of the parties....*" *Johnson v. Manhattan Ry. Co.*, 289 U.S. 479, 496-497 (1993). On this motion, Merck indiscriminately groups Plaintiffs who have not meaningful connection to each other in an attempt to terminate the Fosamax femur litigation. These Plaintiffs did not file their complaints together, they are not represented by joint counsel, and their respective injury dates range over more than a decade. Merck's brief in support of its proposed order acknowledges that the state of the scientific evidence at the time of Plaintiff's injury is centrally relevant to the issue of preemption.[1] The developing science

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[1] *See* Def. Br. at 2 n. 1 (acknowledging that "claims that accrued after the release of the American Society of Bone and Mineral Research ("ASMBR") study on September 14, 2010,

related to Fosamax and femur fractures was not stagnant during the broad time period at issue on this motion (1999 through September 10, 2010). Accordingly, there are different arguments as to why preemption is inappropriate for different Plaintiffs subject to this motion, based on the evolving science at the time of different Plaintiffs' injuries.

C. Even If the Court Enters Merck's Procedurally - Undefined and Constitutionally - Violative Order, Plaintiffs Must be Afforded Sufficient Time to Oppose so That They May Clearly Define the Relevant Plaintiff Groups.

At the very least, if the Court enters Merck's proposed order, Plaintiffs should be permitted sufficient time to respond to Merck's sweeping application, as it cannot be done in the 30 day period that Merck has asked for. The grant of appropriate time to respond does not prejudice Merck. By positioning their motion to dismiss as an order to show cause, Merck has sought to shift the burden to Plaintiffs to come forth with evidence, and Plaintiffs' rights and ability to do so should not be constrained to 30 days. The massive coordination effort contemplated in Merck's proposed order tasks Plaintiffs' liaison counsel with coordinating a unified response amongst the hundreds of separate Plaintiffs and the many different law firms (including referring firms) who represent them. It is virtually impossible to responsibly coordinate such an effort within the 30-day time limit Merck proposes.

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might be subject to a different analysis from that undertaken in *Glynn*.")

In order to respond, Plaintiffs must identify the appropriate plaintiff groups, inform their clients of Merck's application, and prepare coordinated responses based on the different injury groups. Merck does not intend to make the necessary evidentiary showing to support its request to dismiss on an individual basis for each Plaintiff. Failure of the Court to allow sufficient time for Plaintiffs to identify the appropriate groupings with which to respond will result in a grave injustice to Plaintiffs. There is a particularly high risk that, if Plaintiffs are not afforded a fair and reasonable time to respond, the Court will overlook the nuanced differences between the timing of Plaintiffs' claims that are necessary to consider on the preemption issue.

Precisely defining and identifying the commonalties among the Plaintiffs is central to the proper adjudication of their legal claims, particularly in a mass tort litigation. "The [Supreme] Courts emerging view is that the Constitution limits common law tort adjudication to those cases between individual parties or well-defined and carefully-circumscribed groups. Under this new model, it is constitutionally inappropriate for a common law court to adjudicate the rights, liabilities, and interests of persons [...] who cannot be identified or described with a reasonable degree of specificity at the time of the adjudication." Gifford, *The Constitutional Bounding of Adjudication: A Fuller(ian) Explanation for the Supreme Court's Mass Tort Jurisprudence*, 44 Ariz. St. L. J. 1109 (2012).

In determining what issues are proper for an aggregate ruling, courts have a duty to ensure that cases are properly identified and that the germane

evidence on the issue has been fully developed and vetted, so that the ruling affects only those Plaintiffs whose cases are truly related. According to the Manual for Complex Litigation, the ability of the court to identify the common case features and properly issue aggregate decisions depends on the "maturity" of the litigation.

> Litigations are generally considered mature if through previous cases, (1) discovery has been thorough, producing a consensus that the available important information has been provided, (2) a number of verdicts have been received indicating the value of claims, and (3) Plaintiffs claims have been shown to have merit. [...] A "mature" mass tort is one that rests on clearly established law and tested and accepted evidence. [...] In a less mature mass tort, [the Manual warns that] aggregation decisions may be more difficult and may require the judge to obtain additional information. [...] If there are few prior verdicts, judgments, or settlements, additional information may be needed to determine whether aggregation is appropriate. The need for such information may lead a judge to require a number of single-plaintiff, single-defendant, or other smaller trials. [...] As another technique, the judge may stay or defer decisions in the cases before it until more advanced cases or dispositive motions pending in other cases are concluded.

Manual for Complex Litigation, Fourth (2013) § 22.316, Obtaining Information About Common Issues and Case Values.

The Fosamax femur litigation is hardly "mature." Rather, there is new evidence being produced that bears on the preemption issue. Much of evidence on preemption that the Court considered in *Glynn* is heavily contested. Other Plaintiffs have not had an opportunity to challenge Merck's interpretation of the evidence. On a matter of such great magnitude, which potentially affects hundreds of cases in the federal litigation, has broader implications for the larger Fosamax femur litigation, and is of great interest beyond the Fosamax litigation, the Court should proceed with great care, by allowing Plaintiffs a full and fair opportunity to be heard on the issue of preemption.

Conclusion

For all of the foregoing reasons, Plaintiffs respectfully request that the Court deny Merck's application.

Respectfully submitted,

CARELLA, BYRNE, CECCHI,
OLSTEIN, BRODY & AGNELLO

/s/ James E. Cecchi

JAMES E. CECCHI

cc: All Counsel of Record

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August 12, 2013

Via ECF

The Honorable Joel A. Pisano, U.S.D.J.
United States District Court
Court House and Post Office Building
402 East State Street
Trenton, New Jersey 08608

Re: *In re Fosamax (Alendronate Sodium) Products Liability Litigation*
Master Docket 3:08-08 (JAP) (LHG)

Dear Judge Pisano:

Defendant Merck Sharp & Dohme Corp. ("Merck") submits this reply to Plaintiffs' August 5, 2013 letter opposing Merck's request for an Order to Show Cause Why the Claims of Plaintiffs Alleging Injury Prior to September 14, 2010 Should Not Be Dismissed (cited herein as "Pls.' Opp'n").

Plaintiffs argue in their letter that a "show cause" order is procedurally improper and would compromise their due process rights. In effect, Plaintiffs suggest

that the Court and the parties should separately visit the preemption question one case at a time over the next several decades. Plaintiffs' approach would turn the efficiency goals of this MDL proceeding on their head.

The reality is that show-cause orders were designed for precisely the purpose proposed here and that such an order has already been used in this very litigation to accomplish the same result. Plaintiffs' claims of procedural impropriety are therefore frivolous. So too are their invocations of due process. By design, the show-cause approach preserves due process because it affords every affected plaintiff the opportunity to present a basis to distinguish his or her case from the one previously decided (if any such basis exists).

Plaintiffs' objections are particularly improper because they were the ones who selected *Glynn* as the first bellwether trial and promoted the case as being "representative" of the other cases in the litigation. (*See* attached Exhibit A, ECF No. 839,839–1, Plaintiffs' Submission Regarding Bellwether Trial Sections at 4–5.) In fact, in their bellwether trial proposal, Plaintiffs specifically argued that their bellwether trial candidates – including *Glynn* – did "not have case-specific dispositive legal issues and/or [ ] unique factual issues specific to" the particular plaintiffs. (*Id.* at 2.) Thus, Plaintiffs cannot be heard to argue that the preemption ruling in *Glynn* has no relevance to other MDL cases.

Nor is there any reason to heed Plaintiffs' call for more time. As the Court has already recognized, more than enough time has been afforded to all parties to develop a record on preemption. If, for some reason,

any part of this record was omitted from the *Glynn* case (a highly dubious proposition), 30 days provides more than enough time for Plaintiffs to present that evidence to the Court.

A. Entry Of A Show-Cause Order Is Procedurally Proper.

Plaintiffs' contention that a show-cause order "is an inappropriate procedural mechanism for the adjudication of Plaintiffs' claims" (Pls.' Opp'n at 1–2) is precisely backwards. Plaintiffs essentially posit that the same preemption issue should be relitigated in every case, relying largely on the apparent lack of any local rule of procedure expressly authorizing the use of show-cause orders to resolve dispositive issues. (*See generally id.*) This argument makes no sense.

For one thing, it ignores ample on-point case law – including precedent from this very multidistrict proceeding. As Merck's opening brief pointed out, MDL courts routinely use show-cause orders to evaluate whether a ruling in one case is determinative of other member cases. *See, e.g.*, *Schadle v. Qualitest Pharm., Inc.* (*In re Darvocet, Darvon & Propoxyphene Prods. Liab. Litig.*), No. 2:12-159-DCR, 2012 WL 3290145, at *1 (E.D. Ky. Aug. 10, 2012); *In re Allstate Ins. Co. Fair Labor Standards Act Litig.*, No. 2:03md1541, 2009 WL 3011042, at *1 (D. Ariz. Sept. 16, 2009) (Def.'s Br. at 8–9); *see also, e.g.*, *In re Deep Vein Thrombosis Litig.*, No. 04-106 VRW, 2005 WL 1422349, at *1 (N.D. Cal. June 17, 2005) (recounting how court issued order directing plaintiff to show cause why his case should not be dismissed under reasoning in prior preemption order); *In re Sulzer Hip Prosthesis & Knee Prosthesis Liab. Litig.*, 455 F. Supp.

2d 709, 713 (N.D. Ohio 2006) (observing that court entered order directing plaintiffs to show cause why their claims should not be dismissed in light of opinion that dismissed a member case on preemption grounds). Where plaintiffs fail to distinguish their claims from those rejected in such a ruling, courts routinely resolve legal issues and dismiss those claims based on simple application of the prior decision. *See, e.g.*, *Naydeck v. Merck Sharp & Dohme Corp.* (*In re Fosamax Prods. Liab. Litig.*), Nos. 10 Civ. 4831(JFK), 06 MD 1789(JFK), 2013 WL 271741, at *3 (S.D.N.Y. Jan. 24, 2013); *Darvocet*, 2012 WL 3290145, at *1; *Allstate*, 2009 WL 3011042, at *1. And even though local rules do not address show-cause orders in this context (Pls.' Opp'n at 2), the Court has already made clear that it believes such procedures are appropriate by using a show-cause order to apply a dispositive ruling in prior cases – on a preemption issue, no less. (*See* Def.'s Br. at 9 (summarizing this Court's entry of order directing Plaintiffs to show cause why their claims against Generic Defendants should not be dismissed based on prior preemption ruling); *cf.* Pls.' Opp'n at 2 (arguing without relevant citation that an "order to show cause is not an appropriate means to resolve the preemption issue in this litigation").) Plaintiffs do not even attempt to address this on-point precedent.[1]

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[1] Plaintiffs also contend that the Wright & Miller treatise advises against the use of motions to show cause (*see* Pls.' Opp'n at 2), but the same section of the treatise acknowledges that "a request for a show cause order usually will be entertained and treated as a motion, if doing so will not prejudice the opposing parties." 5 Charles Alan Wright et al., *Federal Practice & Procedure* § 1195 (3d ed.).

Plaintiffs' position not only ignores ample case law adopting the show-cause approach but would also destroy the efficiency that is the promise of coordinated MDL proceedings. "The goal of the [MDL] process is to 'promote the just and efficient conduct' of 'civil actions involving one or more common questions of fact' that are pending in different districts." *In re Asbestos Prods Liab. Litig. (No. VI)*, 718 F.3d 236, 243 (3d Cir. 2013) (citation omitted). The aim of efficiency is secured by ensuring that "hundreds or . . . thousands . . . of cases, coordinated, will proceed toward resolution on the merits with less burden and expense overall than were each litigated . . . individually." *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 460 F.3d 1217, 1229 (9th Cir. 2006). Here, a show cause order would achieve that goal. As this Court recognized in *Glynn*, the critical question for preemption purposes is whether "there is 'clear evidence that the FDA would not have approved a change' to the prescription drug's label" prior to a plaintiff's injury. *Glynn v. Merck Sharp & Dohme Corp.* (*In re Fosamax Prods. Liab. Litig.*), Nos. 11-5304, 08-08, --- F. Supp. 2d ---, 2013 WL 3270387, at *7 (D.N.J. June 27, 2013) (quoting *Wyeth v. Levine*, 555 U.S. 555, 571 (2009)) (footnote omitted). The Court held that Merck had produced "clear evidence" to demonstrate that the FDA would not have approved a Warning or Precaution regarding low-energy femoral shaft fractures prior to her injury, and it consequently deemed the plaintiffs' claims preempted. *Id.* The Court's holding in *Glynn* is squarely applicable to other similar cases, and it is far more efficient to resolve that issue in a coordinated manner

than to do so case by case over the course of several years or decades.[2]

In truth, providing each of the "hundreds of litigants . . . an evidentiary hearing" (Pls.' Opp'n at 3), as Plaintiffs propose, would subvert the MDL process. The preemption question is common across the group of plaintiffs identified in Merck's motion and turns on legal questions – not individualized factual ones. Moreover, it has already been resolved after exhaustive deliberation in *Glynn*. Accordingly, the most efficient course is to enter an order to show cause that could potentially dispose of a significant number of cases in this MDL proceeding.[3]

B. Entry Of A Show-Cause Order Fully Comports With Due Process.

Plaintiffs next maintain that "[e]ntry of Merck's proposed order to show cause would constitute an egregious violation of due process and accepted standards for the management of complex litigation"

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[2] Plaintiffs' allusion to the "developing science related to Fosamax and femur factures . . . during the broad time period at issue on this motion" (Pls.' Opp'n at 4), misunderstands the issue. The critical question for purposes of the preemption issue is whether the *FDA* would have approved a Fosamax label that addressed the alleged risks of femoral fracture. Thus the only relevant scientific development was the release of the ASBMR study on September 14, 2010, which prompted the FDA to reconsider label revisions. Plaintiffs have not identified any further evidence suggesting that the FDA would have approved a Warning or Precaution regarding atypical low-energy femoral factures prior to September 14, 2010.

[3] Plaintiffs also complain that Merck did not consult with them prior to filing its motion (Pls.' Opp'n at 1), but Merck knows of no requirement for such consultation, and Plaintiffs cite none.

because it would "deprive Plaintiffs of their fundamental right to be heard." (Pls.' Opp'n at 2–3.) The apparent premise of this argument is that a show-cause order would operate to adjudicate thousands of cases on an aggregate basis without affording individualized consideration to each case. (*See id.* at 3–4.) Not so.

"'[T]he essential requirements of due process . . . [are] notice and an opportunity to respond.'" *Ross v. Duggan*, 402 F.3d 575, 584 (6th Cir. 2004) (quoting *Cleveland Bd. of Educ. v. Loudermill*, 470 U.S. 532, 546 (1985)). Thus, dismissal of a plaintiffs claims does not offend due process as long as the plaintiff is given the opportunity to brief the legal issues and oppose dismissal. *See, e.g.*, *Molosky v. Wash. Mut., Inc.*, 664 F.3d 109, 119–20 (6th Cir. 2011); *In re Bartle*, 560 F.3d 724, 730 (7th Cir. 2009).

For these reasons, MDL courts have rejected due process challenges to show-cause orders intended to facilitate expeditious resolution of constituent cases. In the *Diet Drugs* litigation, for example, the MDL court upheld the use of a show-cause procedure that determined one plaintiff to be ineligible for settlement under a class settlement agreement. *In re Diet Drugs (Phentermine/Fenfluramine/Dexfenfluramine) Prods. Liab. Litig.*, No. 99-20593, 2006 WL 3791338 (E.D. Pa. Dec. 20, 2006). To prove eligibility for settlement, claimants had to submit (among other things) proof of left atrial enlargement. *Id.* at *1. The settlement also provided for an audit of such claims, and in one such audit, the claimant's assertion of left atrial enlargement was rejected, which triggered a show-cause process in which the claimant had to provide evidence proving eligibility for settlement. *Id.* After

the claimant failed to produce credible countervailing evidence and her claim was rejected, she argued that the show-cause process violated her due process rights. *Id.* at *2. The MDL court rejected this claim as "meritless." *Id.* at *3. As the court explained, "[t]he audit and show cause process, as approved by this court, compl[ies] with due process requirements, as claimant has had notice and an opportunity to present her evidence in support of her claim." *Id.*

The show-cause procedure proposed by Merck affords Plaintiffs the same sort of "notice and an opportunity to present [their] evidence." Responding to the show-cause order would give each Plaintiff a meaningful opportunity to fully brief every issue, present any supposed evidence that was not presented in *Glynn* or its aftermath, and identify any ostensible case-specific issues.

C. Thirty Days Is Sufficient Time For Plaintiffs To Respond.

Plaintiffs finally complain that they need more than 30 days to respond because: (1) the tasks of "identify[ing] the appropriate plaintiff groups," informing clients, and "coordinat[ing] responses based on the different injury groups" will be too burdensome in light of the number of parties and law firms involved; and (2) the relevant evidence has yet to be "fully developed and vetted." (Pls.' Opp'n at 5–6.) These arguments lack merit.

First, there are no "different injury groups" (*id.* at 5) or any other material differences among the remaining Plaintiffs with respect to the preemption issue. Notably, while Plaintiffs repeatedly suggest that subsequent cases will present different facts that

will materially alter the preemption analysis, they do not offer any examples of these supposedly different facts. The central preemption question in each case is whether the FDA would have allowed a label revision prior to September 14, 2010. Thus, Plaintiffs' insistence that they must be afforded time to summon "pertinent expert testimony" or other "relevant materials" specific to individual cases (*id.* at 4) is nonsensical.

Second, the notion that the record on preemption is not yet "fully developed and vetted" (*id.* at 5) is preposterous, as evidenced by the fact that it was never suggested prior to the bellwether *Glynn* trial.[4] The issue of federal preemption – and its application to Fosamax Plaintiffs' claims – has been front and center in this litigation since its inception. Plaintiffs have had years to gather evidence related to preemption arguments in the MDL proceeding and in fact did just that. For example, the Plaintiffs' Steering Committee deposed a number of key Merck witnesses whose testimony is relevant to the issue of preemption well in advance of the first bellwether trial in *Glynn*, including: (1) James Adams, a former member of global regulatory affairs for Fosamax at Merck; (2) Dr. Elinor Chen, a Merck regulatory liaison; (3) Dr. Anastasia Daifotis, a former vice president of global medical affairs at Merck with overall responsibility for Fosamax; and (4) Dr. Arthur Santora, Executive Director for the Clinical Development of Fosamax.

Based on this and other evidence identified by the parties, the Court carried out a thorough and

---

[4] Indeed, general fact discovery of Merck concluded on December 31, 2012. CMO No. 10, ¶ 1.2.

deliberate analysis of the preemption question in *Glynn*, hearing arguments and evidence at a month-long trial and through three separate rounds of briefing. *See Glynn*, 2013 WL 3270387, at *5. Shortly before its preemption ruling, reflecting on the months of work by all parties and the Court on the preemption issue, the Court expressed disbelief that any further discovery or development of the record could be required. In the Court's words, the notion that more discovery is required is "'not an argument [Plaintiffs" should be making'" at this point, and "'I don't know what more you want to put in the record.'" (*See* Def.'s Br. at 6–7 (quoting trial transcripts).) Nevertheless, Plaintiffs submitted a nearly 60-page post-trial brief, featuring 62 exhibits, consisting largely of new evidence not presented at trial. *See* 2013 WL 3270387, at *9. Stressing the "several opportunities" given to Plaintiffs "to introduce evidence in opposition to preemption," the Court concluded that Plaintiffs had "not refuted the fact that clear evidence exists" to support a finding of preemption — and that even Plaintiffs' new evidence could not undermine that conclusion. *Id.* Thus, contrary to Plaintiffs' assertion (Pls.' Opp'n at 6), the record on preemption is very "mature" at this stage, and 30 days is ***more*** than enough time to respond to a show-cause order.

In short, there is no good reason to deny or delay the relief Merck seeks. Accordingly, Merck respectfully requests that the Court grant its request for an order to show cause.

Respectfully submitted,

s/ Karen A. Confoy
Karen A. Confoy

Enclosure
cc: Counsel of Record (via ECF)

EXHIBIT A

WEITZ
&
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April 30, 2012

Via Electronic Mail and ECF
The Honorable Joel A. Pisano, USDJ
United States District Court
Court House and Post Office Building
402 East State Street
Trenton, New Jersey 08608

Re: Fosamax MDL 2243; Bellwether Trial Selections

Dear Judge Pisano,

I am writing on behalf of the Plaintiffs to submit the following as the factual summaries of the six (6) selected Fosamax femur fracture cases and to set forth our position regarding which cases are appropriate and representative bellwether trial selections pursuant to Case Management Order 9. Attached is the final submission in this regard.

Very truly yours,

WEITZ & LUXENBERG, P.C.

By: */s/ Edward Braniff*
Edward Braniff

Enclosures (1)

cc: David J. Heubeck, Esq. (w/encl.)
(via ECF and email)

Karen A. Confoy, Esq. (w/encl.)
(via ECF and email)

Christopher Seeger, Esq. (w/encl.)
(via ECF and email)

David R. Buchanan, Esq. (w/encl.)
(via ECF and email)

Paul J. Pennock, Esq. (w/encl.)
(via ECF and email)

James E. Cecchi, Esq. (w/encl.)
(via ECF and email)

Chris Midura, Esq. (w/encl.)
(via ECF and email)

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (No. II) *This Document Relates To All Actions*	MDL No. 2243 Civ. No. 08-08(JAP) (LHG) **Plaintiffs' Submission regarding Bellwether Trial Selections**

Background on Atypical Subtrochanteric and Diaphyseal Femur Fractures

Fosamax (alendronate sodium) is a medication that belongs to a class of drugs known as bisphosphonates. Bisphosphonates are approved for the treatment of certain metabolic bone diseases such as osteoporosis, but have been under serious scrutiny from the pharmacological and clinical communities for some time over the long-term effects they have in bone. In particular, studies have found and it is generally accepted that Fosamax will cause highly irregular, patterned, and thus atypical subtrochanteric and diaphyseal femoral fractures. Before the advent of Fosamax, subtrochanteric and diaphyseal femur fractures were always accompanied by high trauma (*e.g.*, car crashes, accidents, etc.) and were essentially nonexistent in the medical literature because there was nothing unique about such a fracture in the context of such severe trauma. Now, however, they are recognized as fractures that can be and are regularly induced by Fosamax.

Case Selection Factors

The Plaintiffs submit that in selecting appropriate and representative bellwether trial cases there are certain factors that should weigh heavily. It is important that these factors inform the Court, Merck and the Plaintiffs on the fundamental issues of liability and causation across the majority of cases, not a minority of unusual cases. The cases selected should not have case-specific dispositive legal issues and/or a unique factual issues specific to that plaintiff. Cases without unique case specific facts will serve the bellwether purpose by being instructive on a macro level, and not subject the individual case to a potential dismissal or defense verdict because of a unique fact or series of facts. Similarly, if a unique case-specific dispositive legal argument/issue exists, that too should prevent that case from being selected as final bellwether trial case. In the event Merck prevails on such an issue, there would be a nullification of the entire bellwether process as there will be no clearer general understanding of liability and causation. The massive amount of time, personnel, and financial resources expended by the Court and parties will not move the litigation forward, if a case littered with unusual facts and issues of law is selected. All three of the defendants' selections have unusual complications.

In contrast, all three of the proposed Plaintiff cases involve the atypical, subtrochanteric or diaphyseal femoral fractures that plaintiffs' experts opine are the most highly associated with prolonged use of Fosamax. In their review of the aggregated scientific and medical data, plaintiffs' experts are of the view that bisphosphonate-associated femoral fractures most

typically exhibit several features that Plaintiffs believe should also be present in this litigation's bellwether selections. These fractures are usually caused by "low-energy," moderate to no trauma (e.g., fall from standing height or less), are subtrochanteric (below the femoral neck) or diaphyseal (in the femoral shaft), are generally transverse (perpendicular to the femoral shaft), or short oblique (diagonally oriented) in their fracture configuration, are not noncomminuted or if comminution is present, it is minimal (the bone is not "shattered"), and the break usually extends cleanly through both cortices of the bone in a "complete" break (when it does not, incomplete fractures involve only the lateral cortex). Other characteristics that often present with these Fosamax-related injuries include the potential for "beaking" or "flaring" of the lateral cortex (a periosteal reaction to the stress fracture), generalized increase in cortical thickness of the femoral shaft, prodromal dull or aching pain in the groin or thigh appearing weeks to months prior to fracture, bilaterality of the fracture (both legs are often affected), and delayed healing. Plaintiffs would encourage the bellwether selections' fractures to conform with and display as many of these abovementioned criteria as possible.

Also, to be truly representative of the larger pool of cases in this mass tort, the bellwethers should not have unusual and unique co-morbid conditions that defendants can use to either complicate questions of Merck's tort liability or the degree of damages the plaintiff suffered. Plaintiffs urge that atypical medical and social history be avoided in the bellwether selections. Therefore, we respectfully submit that the Court should exclude current smokers and alcoholics,

those currently undergoing chemotherapy or radiation treatment, have metabolic disorders or diseases such as diabetes or have significant genetic, metabolic or endocrine-related bone disorders, are significant users of other complicating medications (glucocorticoids, heparin, or methotrexate, selective serotonin reuptake inhibitors (SSRIs) and proton pump inhibitors (PPIs)). All of defendants' selections have one or more of these unnecessary and inappropriate complicating factors. While such cases can and do present meritorious claims, they are so different from the mass of filings that they should not lead this litigation.

Bellwether Summaries

Below please find the Plaintiffs' factual summary of each of the six (6) bellwether cases, including the facts that render some of these cases more appropriate and representative bellwether trial selections, and the facts of others that make them less instructive to serve as bellwether cases.

***Bernadette Glynn v. Merck Sharp and Dohme Corporation*, MDI, Docket No. 3:11-cv-05304-GEB-LHG**[1]

I. **Personal Background**

Bernadette Glynn was a 54-year-old married mother of two adult children who had been taking Fosamax for six years at the time of her left femoral fracture on April 17, 2009. Mrs. Glynn is a Caucasian women living in upstate New York, perennially traveling to Florida during the winter months with her husband, Richard Glynn. She is a part-time librarian

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[1] Plaintiff's counsel in this case is Perry Weitz of Weitz & Luxenberg, PC.

at a local elementary school and enjoys exercise[2] and the outdoors with her friends and husband.

II. Fosamax Use and Injury

Mrs. Glynn began Fosamax use on March 6, 2003 and testified that she used it continuously until April of 2009. The available records indicate consistent use for weekly dosages from June 28, 2005 to February 22, 2008 whereupon she began generic alendronate use through April of 2009. On April 17, 2009, Mrs. Glynn was carrying items from her garage to the front yard. She testified that she felt a pinch in her left femur, she massaged the area and began to move forward and felt the pinch again. Mrs. Glynn massaged the area again and when she tried to move, she felt pain. She screamed and crumbled to the ground, experiencing what felt like the 'bones rubbing against each other.' She called 911 from her cell phone as no one was home.

Mrs. Glynn was transported to the hospital via ambulance where she underwent open reduction-internal fixation surgery to repair the fractured femur. Following surgery, Mrs. Glynn had extensive physical and occupational therapy during a 4-day hospital stay, 9-day nursing home stay and later at her own residence upon discharge from the nursing home. She still has had residual femur pain and experiences pain in her opposite femur. She has sought the consultation of other physicians for these conditions.

Mrs. Glynn's has a previous history as a smoker of a 1/2 pack per day for 40 years (she quit in the early 2000s) and potentially suffered from

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[2] Plaintiff Glynn regularly engaged in 20 mile or longer bicycle trips prior to femur fracture.

hyperparathyroidism, a condition masked by her Fosamax use.

Mrs. Glynn's case is a very representative case and would be an excellent selection as an initial bellwether trial. Her case involves a low-trauma injury following extensive Fosamax use in which there are no concomitant conditions or medications that compromise her bone quality nor has she sustained previous fractures. She is a young woman with an active lifestyle. This case would help inform the Court, Merck and the Plaintiffs on the very fundamental issues of liability and causation.

***Eleanor On aka v. Merck Sharp and Dohme Corporation*, MDL Docket No. 3:11-cv-05302-GEB-LHG**[3]

I. Personal Background

Eleanor Onaka was a 78-year-old married mother of two adult children who had been using Fosamax for six years prior to her left femoral fracture on June 30, 2009. Mrs. Onaka is a Japanese-American woman living in a single family home in Honolulu, HI with her husband, Harry Onaka. They live near both her son and daughter's families and enjoy spending time together. Mrs. Onaka was previously part-owner and worker in her family-owned grocery in Honolulu. She has additionally traveled and lived in several parts of Asia with her husband, a federal government employee and veteran of American military service during WWII and the Korean War. Both are now

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[3] Plaintiff's counsel in this case is Perry Weitz of Weitz & Luxenberg, PC.

retired and Mrs. Onaka enjoys their family, church volunteer work and her lifelong passion for gardening.

II. Fosamax Use and Injury

Mrs. Onaka filled her first Fosamax prescription for 10 mg daily tablets on February 2, 2003 and switched to 70 mg weekly Fosamax tablets on June 28, 2004. She then began using Fosamax Plus D beginning on November 15, 2006 and continued until she was switched to generic alendronate sodium on August 4, 2009. Mrs. Onaka, at the age of 78, suffered an "atypical fracture of her left femur on alendronate therapy" per her surgical records dated June 30, 2010.

On the day of her fracture, Mrs. Onaka was gardening outside her home. She had been sitting on a gardening stool and picking it up at intervals to move to different locations. When her husband called her to lunch, Mrs. Onaka began standing up from her stool. She heard a loud crack in her left femur and crumbled to the ground, yelling for her husband to help her. She remained in the yard until the ambulance arrived.

After being transported to the hospital by emergency medical staff, Mrs. Onaka underwent open reduction-internal fixation surgery to repair the femur. The femur was reamed from the trochanter extending distally. A titanium rod was then inserted into the femur and attached at the trochanter with a pin to hold it in place. She had an initial 8-day stay in the hospital, and then received physical and occupational therapy during a 12-day stay in a rehabilitation facility. Prior to her discharge from rehabilitation, her family members had to make several alterations to her home due to her injury

including a ramp from ground level to the garage door to facilitate a more fluid transition to her post-surgery life. Today, she ambulates without aid, but is constantly monitored for signs of fracture in her opposite femur.

Eleanor Onaka's case is a very representative case and is a good bellwether trial selection. Her case involves an atypical, non-traumatic femoral fracture following an extended 7½ years of alendronate sodium use, without previous fracture or bone-compromising conditions or concomitant medications. She lives a healthy active lifestyle. This case would help inform the Court, Merck and the Plaintiffs on the very fundamental issues of liability and causation.

***Marilyn Young v. Merck Sharp and Dohme Corporation*, MDL Docket No. 3:11-cv-03225-GEB-LHG**[4]

I. Personal Background

Marilyn Young is a 74-year-old widowed mother of two adult children and grandmother to four grandchildren from San Jose, California. Mrs. Young was prescribed Fosamax for approximately three years prior to experiencing a right femoral fracture. She continued with Fosamax use for another three years and then experienced a second femoral fracture, this time on the left side. Mrs. Young enjoys spending time with her family, gardening and shopping. Each of these passions has been affected by her bilateral femoral fractures.

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[4] Plaintiff's counsel in this case is Dave Buchannan of Seeger Weiss LLF.

II. Fosamax Use and Injury

Mrs. Young was diagnosed with osteoporosis in 2001 and began taking Actonel, another type of the bisphophonate class of drug. She was switched to Fosamax on August, 23, 2003. In February 2006, she switched to Fosamax Plus D which she continued taking until October 9, 2009.

While moving to sit on her couch she sustained a right mid-femur fracture in June 2006. She underwent surgical intervention, received rehabilitation in the hospital for seven days and endured physical therapy upon release. Starting in October of 2006 she began suffering from residual pain in her right leg, which was diagnosed as non-union of her femur fracture. Due to the non-union of her femur fracture, she had to undergo a second surgery in December, 2007, in which the screws of her previous implant were removed. Although she has some pain and limitations that have persisted, her condition has been improving.

However, in June 2009, while walking into her daughter's house, she sustained a second femur fracture. This break occurred in her opposite (left) femur. Treatment included a 3-day hospital stay, surgical repair, and extensive physical therapy.

Although Marilyn Young suffered two Fosamax related fractures, there are other cases among the thousands of Fosamax cases across the country that also suffered two fractures. Despite the dual fractures, it is a representative case and is a good bellwether trial selection. Her case involves an atypical, non-traumatic femoral fracture following just under 5 years of bisphosphonate use, without previous

fracture, followed by another fracture after continued alendronate sodium use. While Ms. Young has been previously diagnosed with Grave's Disease and did take thyroid medication for an extended period prior to and concurrent with her Fosamax use, she has otherwise lived a healthy and active lifestyle.

Defense Selections:

***Ruth Berlin v. Merck Sharp and Dohme Corporation*, MDL Docket No. 3:11-cv-05720-GEB-LHG[5]**

I. Personal Background

Ruth Berlin is 4'9", 135 lbs and recently celebrated her 72nd birthday. She lives in Silver Spring, MD with her husband Arthur. She has three children, each in their 40's. She is a retired elementary school teacher for Montgomery County public schools. She enjoys playing mahjong, traveling, being active, and until suffering her femur fracture, was a member of her church's choir.

II. Fosamax Use and Injury

Ms. Berlin claims Fosamax use beginning in October, 1999, continuing through May, 2011. She began using generic Fosamax in January of 2009. After 2 1/2 years of generic sodium alendronate use, Ms. Berlin suffered a femoral fracture in June of 2011.

Ms. Berlin is not a suitable selection for bellwether trial due to several factors. There are several conditions from which Ms. Berlin suffers. Plaintiff has suffered from endometrial cancer, chemotherapy,

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[5] Plaintiff's Counsel in this case is Dylan Nelson Esq., of the law firm Aaron Levine & Associates.

radiation, and corticosteroid use. These conditions render Ms. Berlin's case an unrepresentative of the currently pending cases.

Additionally, after she was selected as part of the Early Discovery Cases, Plaintiff's counsel discovered that Ms. Berlin had suffered a spinal fracture just prior to her initial Fosamax prescription. Such a significant fracture unrelated to her medication use, would potentially result in the jury deciding this case on unique case-specific issues that do not generally inform on the fundamental issues liability and causation.

***Judith Hoholik v. Merck Sharp and Dohme Corporation*, MDL Docket No. 3:11-cv-05305-GEB-LHG[6]**

I. Personal Background

Judith Hoholik is a retired 73-year-old resident of Perry, Michigan. Mrs. Hoholik is married for 53 years and has four adult children and nine grandchildren. She enjoys spending time with her grandchildren, reading, and crafts.

II. Fosamax Use and Injury

Mrs. Hoholik used Fosamax between March of 2005 and March of 2009. During this period, she sustained left femoral neck fracture on February 2, 2009. Due to the location of the fracture in the femoral neck, not the subtrochanteric area as are the majority of cases, Mr. Hoholik's fracture is not an appropriate bellwether trial case.

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[6] Plaintiff's Counsel in this case is Jonathan Mencel Esq., of the Charles Johnson Law Firm.

More importantly, Mrs. Hoholik claims she only received Fosamax by way of samples from her primary care doctor, and thus there are no pharmacy records available to the parties to confirm her usage, its dosage or duration. Most of the supporting documentation of Mrs. Hoholik's Fosamax use is contained within her personal diary and calendars, and was not fully confirmed by her pharmacy records, doctors' records and doctors' testimony. Although such evidence is more than sufficient for plaintiff to meet her prima facie burdens, there will be "a trial with a trial" on the issue of usage and most cases will not suffer from that deficiency. There will be yet another "trial with in a trial" issue with regard to usage, as to whether she took brand-name Fosamax or generic alendronate during the period the drug was available in generic form, to the date of Plaintiff's injury. The open questions of duration, dosage and use of brand-name Fosamax in Mrs. Hoholik's case renders it a poor representative for bellwether selection.

Beyond the issues of duration, dosage, and use, Mrs. Hoholik is a Michigan resident. Her Fosamax use and injury both occurred in Michigan. The choice of law analysis regarding the application of Michigan's Tort Reform Act might require the Court to engage in a public policy analysis of applying that claim-barring law and perhaps even a Constitutional analysis. Therefore, the choice of law analysis will be far more complicated than in 90% of the pending cases because of the stringent Michigan law purporting to bar personal injury claims for prescription drug injuries.

***Deloris Zessin v. Merck Sharp and Dohme Corporation*, MDL Docket No. 3:11-cv-03918-GEB-LHG; 3:11-cv-03919-GEB-LHG**[7]

I. Personal Background

Deloris Zessin was a 74-year-old, married mother of three who had been taking Fosamax for approximately 10 years before she suffered a left distal femur fracture on April 23rd, 2007. Deloris is an avid golfer. She is a non-smoker who lived with her husband until he passed away in September, 2011. Deloris has a history of lumbar spinal stenosis and osteoarthritis affecting her lower extremities. She has a family history positive for heart disease, cancer and arthritis.

II. Fosamax Use and Injury

Mrs. Zessin claims that she has used Fosamax consistently from October 1997, through December of 2007. Mrs. Zessin testified that her family physician, Dr. Larry Birch, provided her with samples of Fosamax during this time. In late December, 2006, Mrs. Zessin began experiencing leg and muscle pain that increased when walking up stairs. She sought the medical advice of her family physician, who recommended that she see a specialist and was given epidural injections for the pain. On April 23, 2007 Mrs. Zessin fell to the ground while pushing a self propelled lawnmower on her level driveway. She was taken to Faith Regional Hospital, in Norfolk, Nebraska by emergency medical staff. Upon admission, she was diagnosed with a fracture of the

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[7] Plaintiff's counsel in this case is Edward Braniff of Weitz & Luxenberg PC.

femoral diaphysis between the middle and distal third of the femur.

Mrs. Zessin spent four days in the hospital and was discharged on April 27, 2007. She was told to discontinue Fosamax in December of that year, due to concerns relating to osteonecrosis of the jaw. Her pharmacy records indicate that she started taking Evista 60mg tablets on December 12, 2007 afterwards switching to generic alendronate sodium on February 23, 2008.

Mrs. Zessin's medical history complications include: previous hip stress fracture, osteoarthritis, bilateral total knee arthroplasty, calcium and vitamin D deficiencies and a diagnosis of degenerative joint disease concurrent with spinal stenosis. As such, Mrs. Zessin's case is not a representative case and will not inform the Court, Merck or the Plaintiffs in a meaningful way nor will her trial move the litigation forward. The jury will be mired in resolving very unique case-specific issues that do not inform on the fundamental issues of failure to warn, liability and causation.

Conclusion:

The ultimate trial selections should be representative of other cases so that the parties and the Court can achieve the desired results of a bellwether trial. The Plaintiffs strongly urge the Court to select cases that address the fundamental issues of liability and causation, and not those that present issues that are case-specific and/or unique to the given bellwether case.

For the reasons set forth above, the Plaintiffs respectfully request that the Court select the following

three, above-described cases for the trial pool: Bernadette Glynn, Eleanor Onaka and Marilyn Young.

Respectfully submitted,

/s/ Edward Braniff
Edward Braniff

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RECEIVED
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AT 8:30
WILLIAM T. WALSH
CLERK

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: FOSAMAX (ALENDRONATE SODIUM): PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO:** All Actions	**MDL No. 2243** Master Docket No. 08-08 (JAP)(LHG)

ORDER TO SHOW CAUSE WHY THE CLAIMS OF PLAINTIFFS ALLEGING INJURY PRIOR TO SEPTEMBER 14, 2010 SHOULD NOT BE DISMISSED

This MDL consists of products liability suits concerning Fosamax, a prescription bisphosphonate medicine indicated for, *inter alia*, the treatment and prevention of osteoporosis. Plaintiffs in these cases assert state law claims against Merck Sharp & Dohme Corp. ("Merck") – the manufacturer of Fosamax – alleging that Fosamax caused plaintiffs to suffer atypical femur fractures. Plaintiffs' claims all emanate

from a general theory that Merck failed to provide an adequate warning about the risk of such fractures.

On June 27, 2013, after affording the Plaintiffs' Steering Committee ("PSC") and Glynn's counsel repeated opportunities to present their evidence, this Court entered judgment as a matter of law for Merck in the bellwether *Glynn* case on the ground that federal law preempts claims like the *Glynn* plaintiffs' claims against Merck. *See Glynn v. Merck Sharp & Dohme, Corp.*, Case Nos. 11-503, 08-08, --- F. Supp. 2d ---, 2013 WL 3270387 (D.N. Jun. 27, 2013). The Court reached this decision because Merck had presented clear evidence that the FDA would not have approved a Warning or Precaution about low-energy subtrochanteric or femoral shaft fractures in the Fosamax label prior to Mrs. Glynn's injury. *Id.* at *7.

IT APPEARING TO THE COURT, based on all of the evidence presented by the parties in *Glynn*, including the evidence presented at trial, that there is clear evidence that the FDA would not have approved a Warning or Precaution about low-energy subtrochanteric or femoral shaft fractures in the Fosamax label before the American Society for Bone and Mineral Research ("ASBMR") released its first report on bisphosphonates and atypical femur fractures on September 14, 2010; and

IT APPEARING TO THE COURT that the plaintiffs listed in Appendix A to this Order allege they incurred injuries before September 14, 2010; and

IT APPEARING TO THE COURT that the plaintiffs listed in Appendix A assert claims all emanating from a general theory of failure to warn and that the claims

are therefore preempted under this Court's ruling in *Glynn*; and

IT APPEARING TO THE COURT that there is a need to ensure consistency in connection with all complaints that are pending in this MDL,

IT IS on this 13th day of August 2013,

ORDERED that the plaintiffs identified in Appendix A, through their liaison counsel, SHOW CAUSE why their pre- September 14, 2010 injury claims should not be dismissed on preemption grounds pursuant to this Court's ruling in *Glynn* and any briefs and supporting papers shall be filed within ~~thirty (30)~~ 45 days of entry of this order; it is further

ORDERED that Merck shall have thirty (30) days to file a reply to plaintiffs' response to this Order; it is further

ORDERED that the Court may schedule oral argument at its discretion; it is further

ORDERED that plaintiffs' liaison counsel shall ensure that all plaintiffs receive a copy of this Order.

s/ Joel A. Pisano
Hon. Joel A. Pisano
United States District Judge

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (No. II)	MDL No. 2243 Civil Action No. 3:08-cv-08(JAP)(LGH) **DECLARATION OF JAMES E. CECCHI**
THIS DOCUMENT APPLIES TO: **ALL ACTIONS REFERENCED IN EXHIBIT A TO THE COURT'S ORDER TO SHOW CAUSE**	

JAMES E. CECCHI declares as follows:

1. I am a member of the law firm of Carella, Byrne, Cecchi, Olstein, Brody & Agnello, P.C. ("Carella, Byrne"), and am an attorney admitted to practice before this Court. I have personal knowledge of the matters set forth herein. If called as a witness, I could competently testify to the matters set forth herein.

2. I respectfully submit this Declaration in response to the Order to Show Cause.

3. Carella, Byrne and Seeger Weiss LLP are the Court-appointed Co-Liaison Counsel for the Plaintiffs in the above-captioned litigation.

4. Pursuant to the Order to Show Cause, Co-Liaison Counsel and members of the PSC endeavored to reach counsel for all Plaintiffs identified on Exhibit A to ensure that all Plaintiffs received a copy of this Order.

5. Our efforts included, among other tasks, reviewing the master docket and conducting on-line investigations to ascertain counsel email addresses. In addition, my firm placed telephone calls to more than 20 law firms for whom we could not identify an email address and advised them to call my firm and speak with Donald Ecklund if they were not aware of the entry of the Order to Show Cause or needed a copy of this Order. No law firm called in response to our voicemail messages or telephone conversations.

6. Several counsel for Plaintiffs had a clear understanding of the import of the Order and called my office, Seeger Weiss LLP, and Weitz & Luxenberg concerning the practical limitations confronting them and their clients. In this respect, several attorneys expressed concerns that the Order precluded them from filing individual briefs on behalf of their clients despite the fact that Co-Liaison Counsel are not representative counsel for their clients.

7. In addition to contacting counsel to notify them of the entry of the Order to Show Cause, multiple emails were sent and several conference calls were held in an attempt to keep counsel for the Plaintiffs identified on Exhibit A apprised of the comprehensive response that the PSC was preparing and, to the extent practicable, to include them in the response through the inclusion of declarations.

8. The PSC believed that declarations from the affected Plaintiffs, their counsel, and, to the extent available within a 45-day window, treating doctors were necessary, particularly given the absence of any opportunity for the overwhelming majority of these Plaintiffs to pursue any case specific discovery or for their counsel to file responsive briefs on their behalf.

9. I believe that the number of declarations from clients, counsel, and treating doctors would have been greater if additional time had been provided.

10. Attached as Exhibit A is a true and correct copy of the Declaration of Edward Braniff.

11. Attached as Exhibit B is a true and correct copy of Declaration of Carmen S. Scott.

12. Attached as Exhibit C is a true and correct copy of Declaration of Bradley D. Honnold.

13. Attached as Exhibit D is a true and correct copy of Declaration of Troy F. Tatting.

14. Attached as Exhibit E is a true and correct copy of Declaration of Nancy A. Mismash.

15. Attached as Exhibit F is a true and correct copy of Declaration of David P. Dearing.

16. Attached as Exhibit G is a true and correct copy of Declaration of Frank E. Piscitelli, Jr.

17. Attached as Exhibit H is a true and correct copy of Declaration of Tracy A. Finken.

18. Attached as Exhibit I is a true and correct copy of Declaration of Bryan F. Aylstock.

19. Attached as Exhibit J is a true and correct copy of Declaration of Brian A. Goldstein.

20. Attached as Exhibit K is a true and correct copy of Declaration of Evan D. Buxner.

21. Attached as Exhibit L is a true and correct copy of Declaration of Brandon L. Bogle.

22. Attached as Exhibit M is a true and correct copy of Declaration of Calvin S. Tregre, Jr.

23. Attached as Exhibit N is a true and correct copy of Declaration of Sarah J. Showard.

24. Attached as Exhibit O is a true and correct copy of Declaration of Brenda S. Fulmer.

25. Attached as Exhibit P is a true and correct copy of Declaration of Bernard Daskal.

26. Attached as Exhibit Q is a true and correct copy of Declaration of Robert G. Germany.

27. Attached as Exhibit R is a true and correct copy of Declaration of Aaron M. Levine.

28. Attached as Exhibit S is a true and correct copy of Declaration of Charles H. Johnson.

29. Attached as Exhibit T is a true and correct copy of Declaration of Mark A. Tate.

30. Attached as Exhibit U is a true and correct copy of Declaration of Marilyn T. McGoldrick.

31. Attached as Exhibit V is a true and correct copy of Declaration of N. Kirkland Pope.

32. Attached as Exhibit W is a true and correct copy of Declaration of Brian J. Malloy.

33. Attached as Exhibit X is a true and correct copy of Declaration of Roy E. Barnes.

34. Attached as Exhibit Y is a true and correct copy of Declaration of Stuart L. Goldberg.

35. Attached as Exhibit Z is a true and correct copy of Declaration of William B. Curtis.

36. Attached as Exhibit AA is a true and correct copy of Declaration of John D. Sileo.

37. Attached as Exhibit AB is a true and correct copy of Declaration of Richard A. Gurfein.

38. Attached as Exhibit AC is a true and correct copy of Declaration of Peter E. Goss.

39. Attached as Exhibit AD is a true and correct copy of Declaration of Keith Halpern.

40. Attached as Exhibit AE is a true and correct copy of Declaration of David B. Satisky.

41. Attached as Exhibit AF is a true and correct copy of Declaration of John S. Simmons.

42. Attached as Exhibit AG is a true and correct copy of Declaration of Dennis F. O'Brien.

43. Attached as Exhibit AH is a true and correct copy of Declaration of Bobby J. Bell, Jr.

44. Attached as Exhibit AI is a true and correct copy of Declaration of James Zonas.

45. Attached as Exhibit AJ is a true and correct copy of Declaration of James P. Ginzkey.

46. Attached as Exhibit AK is a true and correct copy of Declaration of David P. Matthews.

47. Attached as Exhibit AL is a true and correct copy of Declaration of Brian Cummings.

48. Attached as Exhibit AM is a true and correct copy of Declaration of John David Hart.

49. Attached as Exhibit AN is a true and correct copy of Declaration of Michael S. Pemberton.

50. Attached as Exhibit AO is a true and correct copy of Declaration of Randall E. Smith.

51. Attached as Exhibit AP is a true and correct copy of Declaration of Janet Brooks Holmes.

52. Attached as Exhibit AQ is a true and correct copy of Declaration of Timothy S. Peck.

53. Attached as Exhibit AR is a true and correct copy of Declaration of Jessica E. Vertullo.

54. Attached as Exhibit AS is a true and correct copy of Declaration of Douglas R. Plymale.

55. Attached as Exhibit AT is a true and correct copy of Declaration of Ronald R. Benjamin.

56. Attached as Exhibit AU is a true and correct copy of Declaration of James V. Doyle, Jr.

57. Attached as Exhibit AV is a true and correct copy of Declaration of James J. Rosemergy.

58. Attached as Exhibit AW is a true and correct copy of Declaration of Sarah F. Jubinville.

59. Attached as Exhibit AX is a true and correct copy of Declaration of Moshe Horn.

I declare, under penalty of perjury, that the foregoing facts are true and correct.

Executed on September 30, 2013

/s/ James E. Cecchi
JAMES E. CECCHI

[Exhibit 1 to Ecklund Declaration]

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE:FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (No. II)	MDL No. 2243 Civil Action No. 3:08-cv-08 (JAP)(LGH)
THIS DOCUMENT APPLIES TO: ALL ACTIONS REFERENCED IN EXHIBIT A TO THE COURT'S ORDER TO SHOW CAUSE	

EXPERT DECLARATION OF DAVID B. BURR, PH.D., F.A.A.A.

* * *

1. I, David B. Burr, hereby submit the declaration in support of the Plaintiffs' Opposition to The Order to Show Cause Regarding Federal Preemption. I have personal knowledge of the matter contained in the declaration. If called, I could, and would, testify competently thereto.

BACKGROUND AND QUALIFICATIONS

2. I received a Bachelor of Arts from Beloit College in 1973, and a Master of Arts (1974) and Ph.D. (1977) from the University of Colorado, all in Anthropology.

I was Instructor and Assistant Professor of Anatomy at the University of Kansas before joining West Virginia University in 1980 as Assistant Professor of Anatomy and Orthopedic Surgery. I joined the Indiana University School of Medicine in 1990 as Chair of the Department of Anatomy, a position I held until the end of 2010. I also held a joint appointment in Orthopedic Surgery from 1990–2010, and hold appointments in Biomedical Engineering at Purdue University (courtesy, 2000- present) and Indiana University-Purdue University at Indianapolis (IUPUI, 2002–present). In 2012, I was appointed an Indiana University Distinguished Professor, and I currently serve as the Associate Vice Chancellor for Research at IUPUI.

3. My research activities have included study of the biological and mechanical aspects of age-related bone and cartilage change, bone remodeling physiology using animal models, and human clinical biopsies, and more specifically the causes of skeletal fragility in osteoporosis and in Type 2 diabetes. I have 30 years of experience in studies involving histological and histomorphometric endpoints in both bone and cartilage. I have for many years been a leader in studying the role of skeletal fatigue and microcrack-mediated remodeling in bone biomechanical and physiological adaptation. I am widely considered to be an expert in skeletal biomechanics and remodeling physiology. My laboratory is equipped to characterize histological and dynamic histomorphometric features of different tissues, and to utilize bone density (BMD) and imaging techniques (μCT, pQCT) to analyze tissues in animal models. I was funded by the NIH for over 20 years to do research in these areas, and am

frequently asked to write review articles or book chapters on these topics. I am the author of more than 230 research articles in the peer- reviewed literature, more than 50 book chapters and reviews, and five books on the structure, function and mechanics of bone. Two of these books are highly relevant to this report: RB Martin, DB Burr and NA Sharkey, *Skeletal Tissue Mechanics* (1998) (currently undergoing revision for the 2nd edition), and DB Burr and C Milgrom, eds., *Musculoskeletal Fatigue and Stress Fractures* (2001). I was also a co-Guest Editor with Dr. Graham G. Russell of a special issue of the Journal *BONE* on Bisphosphonates (vol. 49(1), 2011).

4. At the request of the American Society for Bone and Mineral Research (ASBMR) leadership, Dr. Elizabeth Shane contacted me on May 11, 2009 to ask whether I would co-chair the ASBMR Task Force on Subtrochanteric Fractures. I agreed, and Dr. Shane and I proceeded to identify participants for the Task Force, with the approval of the ASBMR. The ASBMR asked us to address several important questions related to these atypical femoral fractures, including to "review carefully the currently available information in order to assess what is actually known and what is not known about atypical femoral fractures and their potential relationship with BP [bisphosphonate] usage." As part of this report, I was one of four members of the Task Force to conduct teleconferences with representatives of companies that market drugs to treat osteoporosis in the U.S. This included Amgen, Eli Lilly, Genentech, Merck, Novartis, and Warner-Chilcott. Our report was subsequently published in the Journal of Bone and Mineral Research in November 2010 (Shane et al.,

2010). I drafted much of the portion of this report that reviewed current knowledge and the potential relationship of atypical femoral fractures (AFFs) to BP usage (pp. 2269–2272 in the final report). This draft was reviewed by all members of the Task Force, and approved. Subsequently, after conferring with several other members of the original Task Force and with ASBMR leadership, it was decided that a review of the original definition of AFFs and an update on the epidemiology and potential pathogenesis of AFFs was warranted. The original Task Force was reconvened, and an update of what is known about AFFs is currently online with the *Journal of Bone and Mineral Research* (*JBMR*, to be published in print early next year, Shane et al., 2014)

5. I was President of the Association of Anatomy, Cell Biology and Neurobiology Chairpersons between 2001–2002. I served on the Executive Board of the American Association of Anatomists (1998–2011), and as its President (2007–2009). I served as Program Chair (2005–2006) and as President (2008–2009) of the Orthopaedic Research Society. In 2004, I became the Director of the Sun Valley International Workshop on Skeletal Tissue Biology, which is now sponsored by the International Bone and Mineral Society ("IBMS"). I remain the Director of the IBMS Sun Valley International Workshop on Musculoskeletal Biology today. The Sun Valley Workshop began in 1965, and is widely recognized to have had a major impact on scientific thinking in the field of skeletal biology particularly in areas related to histomorphometry, in vivo animal models, and biomechanics (www.ibmsonline.org), and receives support from the National Institutes of Health, the pharmaceutical

industry, equipment manufacturers, and other professional societies.

6. I am an Associate Editor for the Journal *BONE* and the *Journal of Musculoskeletal and Neuronal Interactions*, Editor-in-Chief for *Current Osteoporosis Reports*, and serve on the editorial boards for four other scientific journals: *Journal of Biomechanics*, *Calcified Tissue International*, *Osteoporosis International*, and *Journal of Bone and Mineral Metabolism*. I have reviewed manuscripts for 40 different Journals and I typically review approximately 50 submitted articles per year in my field.

7. I am a Fellow of the American Association of Anatomists. I won the Borelli Award, the highest award offered from the American Society of Biomechanics, in 2008; the Glenn W. Irwin Award for Distinguished Faculty Service from Indiana University in 2010; and the Gideon A. Rodan Excellence in Mentorship Award from the American Society for Bone and Mineral Research, also in 2010.

8. A true and correct copy of my curriculum vitae is attached hereto as Exhibit A.

9. I have never testified as an expert witness in any litigation. I am being compensated for my time spent on this matter at the rate of $600 per hour.

10. The opinions expressed herein are stated to a reasonable degree of scientific certainty, based on my education, research, and experience as a researcher in the causes of skeletal fragility in osteoporosis and in Type 2 diabetes. My opinions in this document are further based on my review of the medical literature, various documents provided to me by counsel, and

generally accepted principles of science. The materials I relied upon or reviewed in forming the opinions I express in this declaration are set forth in Exhibit B. I reserve my right to supplement this declaration at a later date based upon receipt of additional information received during the course of the litigation.

II. SUMMARY OF OPINIONS

9. I have been asked by the Plaintiffs' attorneys to consider what Merck knew or should have known at various points in time about the potential for serious insufficiency stress fractures[1] as a result of continuous use of Fosamax. It is my opinion that by the early 1990's, Merck knew or should have known that suppression of bone remodeling could be associated with an increased burden of unrepaired microcracks in bone tissue, and that this could negatively impact bone's mechanical properties.

10. I have also been asked by the Plaintiffs' attorneys to consider the evidence available to Merck at various points in time about Fosamax's association with low energy femoral fractures, including the potential for long-term Fosamax treatment to result in serious insufficiency stress fractures. It is my opinion that the reports received by Merck as well as the

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[1] Herein, I use the term "insufficiency stress fracture" to mean an insufficiency fracture, which the ASBMR Task Force defines as a fracture which is the result of "normal loading of an abnormal or deficient bone," which has as its mechanism of action a fatigue or stress process. A stress fracture results from repetitive loading that overwhelms the body's capacity for repair In using the term "insufficiency stress fracture," I am specifically excluding other types of insufficiency fractures, such as those which may be caused by low bone mass.

scientific data that was being generated by myself and other researchers should have caused Merck to study the association between Fosamax and low energy femoral fractures, including serious insufficiency stress fractures, many years before 2008.

11. I have also been asked by the Plaintiffs' attorneys to consider Merck's efforts to study the potential for insufficiency stress fractures as a result of long-term continuous use of Fosamax. It is my opinion that my studies and those of some of my colleagues between 2000–2006 clearly suggest that suppression of bone remodeling by alendronate was associated with increased microcrack burdens, and moreover that this was associated with significantly reduced bone toughness, and increased bone brittleness that would be consistent with the development of a stress fracture-like lesion. I am not aware of any efforts made by Merck to study this association.

12. I have also been asked by the Plaintiffs' Attorneys to review the material Merck submitted to the FDA on September 15, 2008 to determine whether Merck adequately described the nature of the Atypical Femoral Fracture ("AFF") problem to the FDA. It is my opinion that in several areas Merck improperly characterized the nature of the AFF problem to the FDA, including a failure to describe the potential underlying pathogenesis to the FDA, a failure to inform the FDA that femoral insufficiency stress fractures were rarely seen before Fosamax and other bisphosphonates were available, improperly suggesting various risk factors to the fracture that were not supported by data, and conflating the underlying mechanism of the fracture (stress fracture,

which often doesn't result in a complete break of the bone) with the ultimate outcome (a completed subtrochanteric femoral fracture).

III. THE RELATIONSHIP BETWEEN FOSAMAX, BONE TURNOVER, MICROCRACK, AND STRESS FRACTURE

A. Fosamax, As It Is Designed, Causes a Significant Reduction In Bone Turnover That Has Negative Effects On Bone Tissue Properties

13. Bone is constantly being remodeled in part to maintain calcium balance in the body, and in part to repair and remove microcracks, which are linear cracks that accumulate in the bone matrix as a function of normal activities. Remodeling is a process in which bone is resorbed at a location, and subsequently new bone is deposited at that same location. Usually, the processes of resorption and formation are in balance, but in postmenopausal women, resorption exceeds formation. Over time, this causes bone loss. Therefore, one approach to reducing bone loss is to reduce the overall amount of bone remodeling. .

14. Fosamax, as it is designed, causes a significant reduction in bone turnover, and reduced erosion depth [Boyce et al., 1995; Allen et al., 2010]. Evidence from both human clinical studies and from pre-clinical studies with animals, suggests that treatment with Fosamax suppresses bone remodeling by 70–95% [Chavassieux et al., 1997; Bonnick et al., 2006; Rosen et al., 2005; Mashiba et al., 2000; Allen et al., 2006]. However, the effect of Fosamax and other bisphosphonates (BPs) on bone turnover is highly

location specific and when assessed histologically can differ by an order of magnitude across skeletal sites [see Burr and Allen, 2013 for review of some of these studies]. BPs also exert a time-dependent effect on bone remodeling. For instance, in animal studies, clinical doses of alendronate did not reduce remodeling rate significantly following one year of treatment, but reduced remodeling rates by 85% following three years of treatment [Allen et al., 2006, 2008]. The nitrogen-containing bisphosphonates, such as Fosamax, act both physicochemically and through inhibition of metabolic pathways. The physicochemical action allows bisphosphonates to bind to bone, stabilizing the matrix and preventing its resorption. It has now been shown that BPs not only bind to bone in areas undergoing active resorption, but can enter the bone through canaliculi and can be found on many internal surfaces [Rogers 2009, Turek 2012]. Metabolically, BPs disrupt the cholesterol synthetic pathway from which the prenylated proteins required for osteoclast function and survival are derived. The loss of the resorptive function occurs via inhibition of a key enzyme in this pathway, farnesyl pyrophosphate synthase (FPS), and by prenylation of GTP-ases. Bisphosphonates may not kill all the osteoclasts, but they prevent the remaining osteoclasts from functioning properly.

15. Suppression of remodeling has been shown to increase bone mass, but numerous studies demonstrate that it also creates older bone and negatively affects bone tissue quality. BP treatment is associated with increases in bone mineralization, microcrack accumulation, and alterations in the cross-linking of collagen. Any of these changes, either alone

or in combination, could compromise the mechanical properties of the bone as I will discuss in more detail below.

16. Both pre-clinical and clinical studies show that by reducing the turnover of bone and thereby increasing mean tissue age, BP treatments lead to a significantly higher average tissue mineralization [Boivin et al., 2000; Burr et al., 2003] and lower heterogeneity of mineralization across the bone matrix [Roschger et al., 2001]. Under normal conditions, bone remodeling preferentially renews the more highly mineralized bone matrix. By suppressing remodeling, however, BPs allow more highly mineralized regions to persist for a longer time. Moreover, suppression of remodeling allows more of the newly formed bone to become fully mineralized without replacement. Thus, Fosamax increases the overall mineralization of the tissue by suppressing remodeling and allowing more sites to achieve full mineralization. Increased mineralization will increase both the strength and the stiffness of bone, but increased stiffness is usually associated with reduced toughness [Zioupos et al. 1994, Currey, 2004]. The effect of increased mineralization on reduced toughness has been known for many years [Currey, 1969; Currey et al., 1996; Zioupos, 1998].

17. By reducing bone turnover, and not allowing renewal of the organic bone matrix, BPs permit increased collagen cross-linking. Bone collagen contains both enzymatic and non-enzymatic collagen crosslinks that stabilize the matrix and have significant impact on the bone's mechanical properties. The organic matrix constitutes the principal toughening mechanism in bone and

therefore plays a substantial role in determining properties of energy absorption/toughness [Wang et al., 2002]. Cross-links that are formed through non-enzymatic processes generate advanced glycation endproducts (AGEs) that are associated with tissue that is less tough [Allen et al. 2008], more brittle [Vashishth, 2009] and can sustain less energy before fracture [Viguet-Carrin et al., 2006; Tang et al., 2009].

18. The increased brittleness caused by changes to bone's organic matrix and mineralization allow for greater initiation of microcracks [Allen and Burr, 2007]. In the majority of studies that have documented increased microcracks with BP-treatment, a concomitant decrease in bone toughness has also been quantified [Komatsubara et al., 2003; Mashiba et al., 2000, 2001; Allen et al., 2006; Allen and Burr, 2007]. Microcrack accumulation with BPs is likely the consequence of the increased brittleness and reduced toughness, and not the cause of it. AGEs naturally accumulate in bone as it ages, but under normal rates of bone turnover, they are prevented from accumulating to high levels. However, when bone turnover is suppressed, they can accumulate and make it more likely for cracks to propagate. BPs may exacerbate this effect, particularly in older people who naturally, because of aging, have higher AGEs than younger individuals. The effect is compounded because the BPs impair targeted remodeling more than stochastic remodeling [Li et al., 2001], thereby allowing microcracks to persist for a longer period of time.

B. The Accumulation Of Older Bone Caused By Remodeling Suppression Results In Bone That Is Less Tough And More Susceptible To Microcrack Propagation

19. Studies using animal models have shown repeatedly that the mechanical properties of the tissue, specifically material toughness[2] are reduced with BP-treatment. Following 1–3 years of treatment at doses at or above those used in postmenopausal women, bone toughness in vertebrae and ribs of dogs is 14–33% lower compared to control animals [Mashiba et al., 2000, 2001; Allen et al., 2006; Allen and Burr, 2007]. More recent data show that toughness in BP-treated animals continues to decline with long-term treatment without a significant change in microcrack accumulation or a further increase in mineralization [Allen and Burr, 2007]. This suggests that neither microcracks nor mineralization is completely responsible for the progressive deterioration in the bone's material properties leaving progressive changes to collagen, or the interaction among all these properties, as the cause of this progressive toughness decline.

20. BP treatment is associated with changes in both the initiation and repair of microcracks. This has been demonstrated repeatedly in animal models using various different oral bisphosphonates at doses

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[2] Toughness is a measure of the ease with which cracks in a material can be initiated and can grow. The probability of fracturing from repeated loads is increased with decreased toughness. Stress fractures occur as a result of repeated cyclical loading, as I will explain in more detail below.

ranging from ½ to 6x the dose used for treatment of post-menopausal osteoporosis, and with treatment durations lasting from 1 to 3 years. Significantly more microcracks are consistently noted in the trabecular bone of the lumbar vertebrae and usually in the cortical bone of the rib with BP treatment [Mashiba et al., 2000, 2001; Allen et al., 2006; Allen and Burr, 2007]. Although increased numbers of microcracks also have been noted in the ilium, thoracic spinous process, and femoral neck of dogs treated with bisphosphonates, these sites appear less prone to significant microcrack accumulation (< 2-fold relative to untreated) [Mashiba et al., 2001; Allen and Burr, 2007]. This site-specificity may be important in evaluating damage accumulation in bone from human patients, as such evaluations can only occur from iliac crest biopsies which may underestimate the amount of damage accumulating in the spine or ribs. Recent data from iliac crest biopsies of treatment naïve women and women treated for five years with Fosamax show increased microcrack accumulation with bisphosphonate treatment [Stepan et al., 2007]. Both low femoral neck BMD and increasing age were associated with greater microcrack formation, suggesting that older patients with especially low BMD might be more at risk for damage accumulation. A separate study in which iliac crest biopsies of women treated with alendronate were compared to cadaveric bone showed no significant difference in microcrack levels, although in this study the cadavers used as "untreated controls' were almost 10 years older than the treated patients, and previous drug treatment history was unknown [Chapurlat et al., 2007]. The well-known age-related increase in microcracks [Diab

et al., 2006; Norman and Wang, 1997; Schaffler et al., 1995] and unknown treatment history, therefore, make this an unsuitable control population. The role that bone turnover plays in this accumulation is demonstrated by evaluations in iliac crest biopsies from patients who were pre-treated with alendronate, and then subsequently treated with a course of teriparatide [Stepan et al 2010]. In this case, the microcrack accumulation caused by remodeling suppression was reversed by subsequent administration of teriparatide, and those patients with the lowest BMD had the greatest removal of microcracks. Although this study was not able to conclude that a change in bone turnover rate was associated with this reduction in microcracks, such a conclusion seems eminently plausible.

21. The propensity to initiate microcracks following BP treatment has been shown [Iwata et al., 2006]. Vertebrae from dogs treated for one year with either risedronate or alendronate at doses equivalent to those used to treat postmenopausal osteoporosis in women were subjected to a cyclic loading protocol in compression (5 Hz for 100,000 cycles at loads ranging from 100–300% of the dogs' body weights). Using a double *en bloc* staining protocol with different fluorochromes, this test demonstrated that cracks were significantly more likely to initiate in bone from dogs that had been treated for one year with alendronate, than in those treated either with risedronate or with saline vehicle. This may account in part for the significant and nonlinear inverse relationship between microcrack accumulation and remodeling suppression [Allen et al. 2007]. Cracks are

both more likely to begin following treatment, and their repair is reduced [Li et al. 2001].

C. Less Tough Bone Is More Susceptible To Serious Insufficiency And/Or Stress Fractures

22. Stress fractures are nontraumatic, low energy fractures caused by repeated applications of loads below the fracture threshold. They occur in a variety of skeletal locations commonly in physically active people. They are generally the result of the gradual accumulation of microcracks in bone until the cracks coalesce and can be visualized radiographically or scintigraphically [Burr, 1997; Burr and Milgrom, 2001]. The term "stress fracture" often applies to fractures resulting from excessive loading of a normal bone. An insufficiency stress fracture, on the other hand, is used to connote a fracture caused by normal loading of a bone that has poor quality and material properties.

23. Bone that is less tough can either initiate more microcracks, or allow them to grow and coalesce more quickly. Although the formation of a microcrack will dissipate energy and delay fracture, once the crack is formed, the residual mechanical properties of the tissue are reduced. It has been shown that the presence of microcracks in bone reduces strength [Burr et al., 1997; Burr et al. 1993], reduces the elastic modulus of the tissue (by definition, a reduction in elastic modulus is the criterion used by engineers to define damage in many materials) [Burr et al., 1998], and reduces toughness [Mashiba et al., 2000, 2001].

D. Toughness, Not Strength, Is The Critical Material Property When Assessing Propensity For Stress Fracture

24. Strength and stiffness are often used to define the health of a bone, but they are not so clearly, or physiologically, related to risk of fracture as the amount of energy required to cause fracture. A bone that is strong and stiff may require much less energy to fracture than a bone that is weaker and more compliant. Bone mineral density is highly correlated with strength and stiffness [Currey, 2002], but there is a more complex relationship between BMD and the energy required to cause fracture. For instance, highly mineralized osteopetrotic bone is very stiff and very strong, but also very brittle, resulting in failure with lower energy, and increased risk of fracture. The modulus of toughness of a bone is a measure of how much energy is required to cause the bone tissue to crack. Lower modulus of toughness, therefore, indicates that the bone can fail at lower energy, and is often associated with a brittle-type fracture. The probability of fracturing from repeated loads is increased with decreased toughness. It has been shown [Currey, 2004] that stiffness and toughness are usually inversely related in bone, so that increased material stiffness (modulus) may signal reduced energy to fracture (toughness).

IV. MERCK KNEW AS EARLY AS 1990 THAT CONTINUOUS USE OF FOSAMAX COULD MAKE BONES SUSCEPTIBLE TO SERIOUS INSUFFICIENCY AND/OR STRESS FRACTURES

25. In 1990 in an Operational Plan related to Phase I and IIa studies, Merck posed the question "What would be the undesirable consequences of excessive suppression of bone resorption by MK-217?"[3] They contended: "Microscopic fractures occur in normal bone due to the mechanical stress of normal activity. The bone remodeling process eliminates these fractures through local bone resorption and formation of new bone. If MK-217 inhibits the remodeling process too greatly, inadequate repair may take place. Both nonclinical and clinical studies will address this question by assessing bone strength in treated animals, and bone histology and histomorphometry in MK-217-treated humans and animals." [MRK-FOSNJ-SAN-00557997]

26. In April 1990, in a memo to the MK-217 Product Team, Dr. BJ Gertz stated: "The consultants . . . did question whether chronic reductions in bone turnover would increase the risk of stress fractures, i.e., an effect on bone quality. The two year dog study will address that question." [MRK-FOSMDL-00897340] After searching the available literature, I have been unable to locate a published 2 year dog study that evaluated the change in mechanical properties in dogs treated with Fosamax. One study in ovariectomized nonhuman primates [Balena et al., 1993] was

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[3] MK-217 is the internal identification used by Merck for the compound that was later named Fosamax.

conducted by Merck, but only measured femoral strength and stiffness. This is an incomplete characterization of the mechanical integrity of bone. As indicated before, the more relevant parameters for assessing the potential risk for fracture, in my opinion, are energy to fracture and toughness, neither of which were measured by Merck in the Balena study.

27. In a separate memo in May 1990 from CP Peter, the consultants recommended that bone quality in chronically treated dogs, rats, baboons and pigs be assessed, and that such an assessment address the concerns about stress fractures adequately. They also recommended that bone scintigrams be made to evaluate the possible occurrence of stress fractures. [MRK-FOSNJ-SAN-00541807] I am unable to find a published study from Merck in which bone quality was assessed in dogs chronically treated with alendronate. From other documents (March 1991), it appears that the canine study was a fracture healing study and was only 25 weeks long, inconsistent with "chronic" exposure. In any event, it is surprising in light of this recommendation made by several experts in the field (Drs. Kaplan, Kleerkoper, and Einhorn) that in the nonhuman primate study reported by Balena et al. [1993], which could have begun to address this question, only bone strength, not mechanical measures of bone quality, were measured. Reasonable scientists at this time should have known that mechanical measures of bone intrinsic (material) properties were necessary measurements in assessing the risk of fracture.

28. In April of 1991, Dr. Henry Bone expressed his concern that MK-217 could produce a "profound suppression of bone resorption so that micro-fractures

would not heal." [MRK-FOSMDL-00897472] He suggested a dose response study in patients older than 70 years.

29. In July of 1991, in response to a letter from Dr. Gideon Rodan posing questions about the risk/benefit ratio of decreased bone turnover by a "resorption inhibitor," and the level of turnover suppression that could be considered "safe," Dr. Michael Parfitt stated: "The main risk of reducing turnover would be an increase in bone age. The expected consequences of this would be increased osteocyte death, hypermineralization, increased brittleness and accumulation of fatigue damage because of increased production and decreased repair." [MRK-FOSNJ-SAN-00541788] Although stressing that these were purely theoretical considerations, it is my contention that this should have sensitized Merck to the possibility of the negative mechanical effects of increased bone age at least beginning with the first reports by Mashiba et al. in 2000, 2001.

30. The Project Term minutes from August 13, 1991 conclude from Dr. Parfitt's statements that "there should be no concern regarding the possibility of 'freezing' bone while receiving alendronate therapy at the therapeutic doses." [MRK-FOSMDL-00897641] Although Dr. Parfitt stated that reducing turnover to the lower end of the reference range for healthy premenopausal women would leave a comfortable margin for safety, most reasonable scientists would conclude that a significant reduction in bone turnover rate would increase bone age, with the consequent negative effects stated by Dr. Parfitt.

31. In August of 1991, the potential negative effects on bone mechanical properties caused by suppression of remodeling specifically with bisphosphonates, was a topic of discussion at the International Sun Valley Hard Tissue Workshop. On the final day, during a summary and synthesis of the meeting, this was discussed in detail, and the general consensus was that this could be a problem. I recall this because it was at this meeting that I realized that experiments needed to be performed to address this potential negative effect of remodeling suppression. It was key to my future work. Dr. G. Seedor and Dr. Gideon Rodan from Merck, as well as Dr. Donald Kimmel, who was then at Creighton University but was eventually employed by Merck, attended this meeting, as did other Merck advisors such as Dr. Robert Recker.

32. Early in 1995, I wrote the following in Project 3 of Dr. Conrad Johnston's Program Project Grant ("Some Determinants of Bone Mass in the Elderly"):

> "The **primary goal** of this proposal is to determine whether treatment with an agent that reduces bone turnover significantly (e.g. bisphosphonates) will increase bone fragility. A **second goal** is to determine how much bone remodeling can be inhibited before bone strength is compromised. A **third goal** is to determine whether bisphosphonate treatment reduces bone strength by allowing microcrack accumulation, inhibiting mineralization of new bone, or through a combination of these. Whether spontaneous fractures occur or not, the effects of bisphosphonate treatment on microcrack and osteoid accumulation, and by extension their effects on strength, need to be documented

because of questions raised by earlier animal studies (Flora et al., 1980, 1981; and human clinical trials (Storm et al., 1990; Watts et al., 1990).

"Questions have been raised regarding the effects of reducing bone turnover on the mechanical integrity of bone. These discussions have influenced the FDA decisions about guidelines for drugs for the treatment of osteoporosis. In most cases a reduction in bone turnover is associated with increased bone mass and decreased fracture risk (e.g. the effects of estrogen therapy). It has been reasoned that marked reduction in turnover may be damaging, but this is only supported by animal experiments with etidronate (Flora et al., 1980, 1981). These experiments have not been repeated. It is important to know the influence of bone turnover on mechanical integrity and such data are not currently available."

One of the reviewers on the NIH review panel for this project was Dr. David Dumpster. The proposal was deemed important, and subsequently funded. This is the work that eventually was published by Mashiba et al. [2000, 2001]. Therefore, by early 1995, it is clear that investigators in the scientific community were aware of the possibility that remodeling suppression could negatively affect bone mechanical properties and it was deemed important enough that an independent review panel convened by the NIH felt it was worthy of funding.

33. At a Merck consultants' meeting in 1997, a consensus was achieved that "change in bone density

is not an adequate surrogate for fracture risk and therefore none of the currently available surrogates can substitute for fractures as measures of efficacy." [Exh. 1.1876 (P000001876)] Given this statement, it is my contention that Merck should have sought data on mechanical properties of bone following alendronate treatment from animal studies (as these are not possible to perform in humans).

34. In December 1997, it was affirmed that the then-proposed FLEX trial could not answer "one important question: Longer-term alendronate could be more detrimental than placebo." [Exh. 1.1879 (P000001879)] It is surprising that at least seven years after the question of the potential detrimental effects of alendronate was raised, this important question had not been answered by any studies performed by Merck.

V. ALTHOUGH AWARE OF THE POTENTIAL FOR SERIOUS INSUFFICIENCY STRESS FRACTURES WITH FOSAMAX TREATMENT, MERCK IGNORED A GROWING BODY OF DATA ESTABLISHING THE CONNECTION

A. Numerous Animal Studies Showed The Connection Between Fosamax Use and Microcracks

35. In 2000, Mashiba et al. published a paper showing that treatment with high doses of alendronate for only one year resulted in a significant increase in bone microcracks, and a significant reduction in bone toughness, in the *cortical bone* of the rib.

36. The following year, Mashiba et al. [2001], showed that treatment with high doses of alendronate for only one year resulted in a significant increase in bone microcracks, and a significant reduction in bone toughness in the lumbar vertebrae, a primary site for osteoporotic fractures.

37. In 2003, Komatsubara et al. published a paper in which dogs were treated with a different bisphosphonate, incadronate, for three years. This work showed that BP treatment for a prolonged time was associated with a significant increase in microcracks, and a 40% reduction in intrinsic modulus of toughness in lumbar vertebrae. This toughness reduction was about twice what Mashiba et al. [2001] found following one year of treatment with alendronate. Subsequently, Komatsubara et al. [2004] reported a significant increase in microcracks in cortical bone from the rib of dogs treated with incadronate, but this was not accompanied by reduced toughness. This was confusing, and I discussed this work with one of the senior authors (Dr. Satoshi Mori) to determine how they had calculated modulus of toughness. They could not explain how the calculation was performed, as the value had been generated by system software. It was unclear to me at the time that they had corrected accurately for the increased bone volume that was associated with bisphosphonate treatment. As I could not verify the method of calculation for modulus of toughness, I have continued to view this work with skepticism.

38. Following publication of the Mashiba papers, there remained a question about whether bisphosphonates suppressed both stochastic (i.e. random) remodeling generally associated with calcium

metabolism, and remodeling targeted specifically to repair microcracks. This was highly relevant to the question about whether bisphosphonates prevented crack repair. Some scientists at the time believed that bisphosphonates might suppress overall turnover, but allow the repair of microcracks. We designed a study and consulted with Dr. Michael Parfitt about our experimental design. We reported the results of this study in a paper by Li et al. [2001], in which dogs were assigned to control, risedronate-treated, or alendronate-treated groups. In the control group, we found three times more associations between cracks and resorption spaces than expected, indicating that remodeling normally targets cracks for repair, validating our earlier studies [Burr and Martin, 1993]. By contrast, although there was an increased damage accumulation in the bisphosphonate-treated groups, fewer cracks than expected were associated with resorption spaces, indicating that suppression of remodeling significantly suppressed the targeted repair of microcracks. The number of observed associations of cracks and the maximum number of potential associations was not different than 1.0. This means that the bisphosphonates eliminated targeted remodeling (ie, the repair of damage), and that any remodeling apparent in the bone was incidental to the repair of damage. We concluded: "Although the accumulation of cracks in bisphosphonate-treated dogs could also be a function of increased tissue mineralization and increased mean tissue age associated with global remodeling suppression, these data further suggest that the complete suppression of targeted remodeling could account for this increased microcrack burden."

39. It is clear that Merck investigators discounted this data in a deprecating way. In internal memos, Dr. Rodan referred to "this whole turnover microcrack imaginary monster" (March 21, 2001) and later characterized our results as "the so-called microcrack, defined by the fuchsin stain . . ." (March 31, 2001) [MRK-FOSMDL-DAI-00032511]. In another email, Merck employee John Orloff stated that "bone 'toughness', which was found to be significant in the Burr paper, is a convoluted and derived biomechanical parameter that depends on the directly measured biomechanical parameters which were not found to be significant." (March 20, 2001) [MRK-FOSMDL-SAN-00064649].. Merck ignored our data and, instead, sought to downplay it by stating that "so far there is absolutely no evidence that treatment up to 7 years has any deleterious effect . . . ." Mr. Orloff concludes his email by stating that "some of these people really irritate me."

40. Subsequently (August 21, 2001), Merck scientist Dr. Santhanagopal, stated "Based on what we know theoretically, [Burr's] contention is correct." He also cites work in 1994 by Peter Zioupos that "conclusively [shows] that the phenomenon of yield and damage in bone is due to 'microcracking' of the bone material." [MRK-FOSMDL-PEV-00025671]

41. In late 2001, I wrote the following statement in a grant proposal that was subsequently funded and formed the basis for papers showing that clinical doses of alendronate also will cause increased accumulation of microcracks and, over a three year treatment period, a 27% decline in vertebral toughness:

"Bisphosphonates increase bone mass and decrease vertebral and non-vertebral fracture incidence in postmenopausal osteoporotic women [Black et al., 1996; Ensrud et al. 1997; Karpf et al., 1997; Cummings et al. 1998; Eastell et al., 1999; Watts et al., 1999] by reducing the activation frequency of new bone remodeling and by reducing resorption depth [Steiniche et al., 1991; Storm et al., 1993; Balena et al. 1993; Chavassieux et al., 1997; Balena et al., 1996; Motoie et al., 1995]. They are effective because they inhibit bone remodeling, preventing the loss of bone that occurs through resorption and allowing refilling of the remodeling space. However, in doing so they also may prevent the repair of microdamage [Mashiba et al. 2000, 2001; Hirano et al., 2000]. Animal and post-mortem human studies show that microdamage accumulation in bone will reduce the elastic modulus of the tissue [Schaffler et al., 1989; Keaveny et al., 1994; Jepsen and Davy, 1997; Burr et al., 1998; Pidaparti et al., 2000], will decrease bone strength [Burr et al., 1997], and can increase energy dissipation [Pattin et al., 1996] when bone is loaded.

"We recently showed that an 85–95% decrease in activation frequency (Ac.F) in trabecular bone of the lumbar vertebrae, or a 53–68% decrease in Ac.F. in the cortical bone of the rib, is associated with a 2–3 fold increase in damage accumulation [Mashiba et al., 2000, 2001]. In both cases, damage accumulation to these levels was associated with a 20% decrease in tissue toughness (the amount of energy required to

cause the bone tissue to fail). It is not known whether the rate of microdamage accumulation will accelerate with continued suppression of remodeling, or whether it will reach an asymptote that signals a new balance between remodeling and damage. Nor is the appropriate balance between remodeling suppression and effective repair of damage known."

42. These funded studies resulted in the paper by Allen et al., [2006] which showed that microcrack accumulation in the vertebrae of dogs treated with alendronate or risedronate at clinical doses for one year was significantly increased compared to vehicle-treated dogs. This work showed a 14% reduced toughness in the vertebrae of these animals, which was not statistically significant probably because of low statistical power. This work also showed that damage accumulation in the lumbar vertebrae was negatively and nonlinearly associated with reduced bone turnover, measured by activation frequency. In other words, the greater the suppression of bone turnover, the more damage accumulated in the tissue.

43. This was followed in 2007 [Allen and Burr, 2007] by a paper showing an increase in microcrack density in dogs treated at clinical doses for three years which was not statistically significant. However, this paper also showed a statistically significant 27% decline in bone toughness in dogs treated with clinical doses of alendronate compared to controls, and a statistically significant reduction in bone toughness in dogs treated at higher doses.

44. In 2004, we embarked on a trial to determine whether short-term suppression of bone turnover

using bisphosphonates (in this case, risedronate) could prevent or delay the onset of stress fractures in Israeli soldiers undergoing basic training [Milgrom et al., 2004]. Our expectation was that a short period of treatment would suppress the initial loss of bone during remodeling targeted to repair microcracks in a group known to have high rates of stress fractures, and that it would prevent or delay the onset of stress fractures. Because of a high dropout rate, statistical significance could not be demonstrated, but the results showed that the soldiers treated with bisphosphonate had a higher incidence of stress fractures of the femur, tibia and metatarsus.

B. Beginning in 1998, Merck Began to Receive Reports of Unusual Femur Fractures Which Should Have Triggered Merck To Study The Connection Between Fosamax and Insufficiency-Type Femur Fractures

45. As early as 1999, Merck began to receive Suspect Reaction Reports from the medical community indicating that physicians were seeing patients who had been taking Fosamax present with long bone fractures.

46. In 1999, Merck received a report of a female patient who had been taking Fosamax and who had developed "insufficiency fracture[s] in both of her thigh bones, which were not caused by trauma, and which were associated with thigh pain." [MRK-FOSMDL-01337515]. This report illustrates a classic example of what was likely bilateral incomplete atypical femoral fractures ("AFF") in this patient. Indeed, in this report, the patient had prodromal pain

in her "thigh bones" (this is the same as the femur). Prodromal pain is associated with stress fractures and is one of the minor features of an atypical femoral fracture. The fractures were also bilateral, and associated with no trauma, both additional features of AFFs. Furthermore, the bilaterality of the fractures strongly suggests a pathologic process occurring in the bones, as opposed to a traumatic event. A report like this is fully consistent with the potential adverse consequence of continuous treatment with Fosamax that Merck had been alerted to years earlier.

47. In 1999, Merck received a report of a 53-year old female patient who "developed bilateral femoral fractures in the absence of trauma." The reporter indicated that the patient "had normal spine bone mineral density and slight osteopenia at her hip." [MRK-FOSMDL-01337513]. This report is further evidence of non-traumatic bilateral femoral fractures in a patient taking Fosamax. Importantly, this patient did not have osteoporosis. As with the previous case, the bilaterality in this case is suggestive of a pathologic process. Although the warnings Merck received years earlier about the possibility for insufficiency stress fractures after Fosamax treatment were not site-specific, these reports should have provided a clue to Merck that further study of unusual femoral fractures in people and bone mechanical properties in animals models were needed in light of its preexisting knowledge of, and warnings from advisors about, the potential for stress fractures with Fosamax treatment.

48. In 2000, Merck received another report regarding a 77-year old female who developed "a spontaneous femoral fracture." This woman's fracture

had been preceded by complaints of pain while walking (i.e. prodromal pain). [MRK-FOSMDL-01337511]. A "spontaneous" fracture also suggests that this was a low energy fracture without trauma. Again, the absence of trauma, the involvement of the femur, and the prodromal pain prior to fracture, all characteristics of AFFs, should have alerted Merck that Fosamax use may have been involved in predisposing to these femoral fractures. These clues should have caused Merck to further study this potential, particularly in light of its prior knowledge and advice from consultants.

49. In 2002, Merck received a report of two female patients who had "stress fractures on tension surfaces . . . of their femurs that have not healed." The physician who made this report asked Merck the correct questions: "Is decreased osteoclastic resorption also contributing to decreased coupled osteoblastic formation? Would this limit healing potential of stress fractures?" [MRK-FOSMDL-01337516]. This report was generated by a physician who was treating more than one patient who had developed femoral stress fractures subsequent to Fosamax use. Merck had been alerted to the possibility of such fractures over a decade before. By 2002, Merck had received multiple reports of this type of fracture *in the femur*. Merck should have designed a study to investigate the potential for long-term Fosamax use to cause insufficiency stress fractures in the femoral shaft.

50. In 2003, Merck received a very detailed report of a 59-year old woman who had developed bilateral stress fractures after at least five years of Fosamax treatment. The woman had normal bone mineral density at her hip, although she had a previous spinal

compression fracture. In 2002, the physician noted that an MRI showed a "diffuse/poorly defined focus of intense edema within the intramedullary cavity of the proximal left femoral shaft and thickening of cortical margin of the outer left proximal femoral shaft." This finding is consistent with a stress fracture on the left femur in a patient with cortical thickening. Because cortical thickening should normally be associated with increased bone strength and stiffness, this should have caused Merck to question whether the intrinsic material properties of the bone tissue were negatively affected by Fosamax. Later in 2002, a bone scan revealed "increased . . . uptake in the proximal left femur which may have represented a fracture or a tumor." By 2003, a bone scan showed that the stress fractures were now bilateral in both femurs. In 2006, the physician concluded that the fractures "may be due to hypermineralization due to long term use of alendronate sodium." [MRK-FOSMDL-01337531]. This report provided Merck with the most clues to date about Fosamax's potential to cause insufficiency stress fractures in the femoral shaft. The reporter noted many of the classic signs of an AFF: prodromal pain, bilaterality, and radiographic evidence of a stress fracture based on a positive bone scan. A reasonable scientist who was aware of Fosamax's potential for causing insufficiency stress fractures would consider these reports important and take steps to develop more scientific evidence to further examine Fosamax's role in causing serious femoral shaft insufficiency stress fractures that could progress to a complete fracture.

51. In 2004, Merck received information regarding an abstract presented by Dr. Clarita Odvina and

colleagues of several patients with unusual fractures who had suppressed bone turnover. [MRK-FOSMDL-01337552]. Several of these patients had low trauma fractures of their femur, including two patients with bilateral femoral fractures after 5 and 8 years of treatment with Fosamax, respectively. As noted in the adverse experience report submitted by Merck to the FDA, "[t]he authors commented that femoral shaft fractures were rare even in patients with osteoporosis. Therefore, the occurrence of femoral shaft fractures in the four patients on long term bisphosphonate therapy raised the possibility that such treatment might be associated with spontaneous unusual fractures." At this point in time, Merck had a large amount of data which suggested that Fosamax was associated with unusual femoral shaft fractures, including insufficiency stress fractures of the femur.

52. In 2005, Merck received a report from Dr. Joseph Lane, a respected doctor and scientist who is a member of the ASBMR Task Force on atypical femoral fractures, of "25 patients with long bone fractures that [*sic*] have taken Fosamax . . . for a long time. He also reported that 100% of patients in his practice who have experienced femoral fractures (without being hit by a taxicab), were taking Fosamax . . . for over 5 years. At [his] hospital they call it the 'Fosamax Fracture.'" Later in that report, Dr. Lane reported to Merck that bone biopsies of these patients show that the "bone is asleep and there is a subset of people who are over-suppressed . . . ." Dr. Lane also reported to Merck that his hospital (the Hospital for Special Surgery in New York City) was planning a study "to look at long bone fractures in patients who were treated with Fosamax . . . versus a control group who

was not." [MRK-FOSMDL-GOL-00012457-00012460]. In that same email, Merck identified another report by Dr. Lane in which he identified a woman in her 70's who had been experiencing thigh pain and later broke her femur after taking Fosamax for 7 years. I am not aware of any efforts Merck made to obtain more information on the 25 fractures reported by Dr. Lane. Certainly by this point in time (if not much earlier), Merck had ample data to suggest that Fosamax was associated with or contributing to a particular kind of femoral shaft fracture.

53. These reports, combined with Merck's prior knowledge of the potential for insufficiency stress fractures associated with long-term Fosamax use, should have caused Merck to study this serious problem.

C. Merck's Internal Data Apparently Provided Clues To This Developing Safety Signal

54. I reviewed the expert report prepared by David Madigan, Ph.D. Dr. Madigan purported to "examine whether a signal of problematic oversuppression of bone turnover and associated atypical femur fracture syndromes existed for Fosamax . . . ." I am not an expert in pharmacovigilence or bio-statistics and, as such, I have no opinion on whether the methods and techniques Dr. Madigan used are sound or valid. However, in the context of my prior opinions regarding what Merck knew about Fosamax's potential for causing serious insufficiency stress fractures, certainly a data signal for "femur fracture" and "stress fracture" should have alerted Merck to more fully study the question that was first raised by outside and

inside scientists in the early 1990's. The search terms used by Dr. Madigan for adverse events were those "selected by Merck to internally evaluate the same." Dr. Madigan's report shows that the signal for a stress fracture in those taking Fosamax first emerged in 2003, and the signal for "femur fracture" first emerged in 2005. Furthermore, the signals Dr. Madigan detected for delayed union, malunion, and nonunion, while not directly attributable to Fosamax treatment, are indicative of a kind of fracture that is difficult to heal such as an atypical femoral fracture, and first emerged as a signal in 2002.

D. Merck Failed To Adequately Study The Potential For Long Term Fosamax Use To Cause Serious Insufficiency Stress Fractures

i. Bone Material Property Testing

55. There are a number of biomechanical parameters that can be used to characterize the mechanical integrity of bone. The key relationship is that between load applied to a structure and displacement in response to the load. The slope of the elastic region of the load-displacement curve represents the extrinsic stiffness of the structure. Besides stiffness, strength can be derived by measuring the maximum force at failure, and work or energy to failure can be calculated by measuring the area under the load-displacement curve. Each of these measured parameters reflects a different property of the bone: maximum force reflects the general integrity of the bone structure, stiffness is closely related to mineralization, and energy to failure is the amount of energy necessary to break the bone. The

biomechanical status of bone is poorly described by any single one of these parameters. For instance, a very stiff bone can also be very brittle and break easily. When load and deformation are normalized for the amount and distribution of bone by engineering formulae, a stress-strain curve is generated which allows the calculation of intrinsic, or tissue-level, strength (ultimate stress or strain), stiffness (elastic modulus) and the modulus of toughness (energy to failure). These concepts are described in more detail in Turner and Burr [1993, 2001].

ii. How Does One "Properly" Test Bone Toughness?

56. It is also possible to test bone toughness in a different way using techniques associated with true fracture mechanics. The goal with these techniques is to describe the fracture process in a material, without regard to its geometry. It allows one to test the probability that a crack may be initiated in a material, and the probability of it growing to a critical size. A fracture mechanics test produces two key parameters: the critical stress intensity factor, K_c, and the critical strain energy release rate, G_c. K_c is also known as fracture toughness, but is different than the modulus of toughness. Both toughness and modulus of toughness are acceptable mechanical tests to evaluate the properties of a material, including bone tissue, but they provide different information. Fracture mechanics tests are better for defining the relationship between the local stress field near a crack tip and the subsequent growth of the crack. Modulus of toughness provides a measure of the amount of energy that is required to cause tissue failure, irrespective of geometry or bone mass.

iii. Merck Failed To Do Mechanical Testing Of Bone After Long Term Use Of Fosamax

57. Merck investigators measured bone strength of both cortical (from the radius) and lumbar vertebral bone in several studies using large animal models [Peter et al., 1996; Balena et al., 1993]. However, they calculated only strength in the Balena study, and only strength and stiffness in the Peter study. A single mechanical measure is insufficient to fully characterize the mechanical integrity of a bone, for reasons stated above. It would have been relatively easy to also calculate energy to fracture and to convert the load-deformation curve to a stress-strain curve to calculate ultimate stress, modulus of elasticity and modulus of toughness, but this was not done. Therefore, it is my opinion that Merck investigators did a poor job of characterizing bone mechanical quality, particularly after recognizing that suppression of remodeling could have significant deleterious effects. Moreover, the Peter study was only a 25 week study in which the primary outcome was related to fracture healing. This is an insufficient amount of time to see significant changes with treatment in a dog (about 2 remodeling cycles, which would be equivalent to about 8 months of treatment in a human).

E. Summary

58. Therefore, it is my contention that:

a. By 1990, Merck knew that fractures, including stress fractures, due to inadequate microcrack repair could be a cause for concern.

b. By 1991, many scientists recognized the potential problem that suppression of bone turnover could impair mechanical properties of bone.

c. By 2000, it had been proven with statistical confidence that suppression of bone turnover by alendronate impaired the mechanical properties of bone, including bone modulus of toughness, a critical property in assessing a bone's susceptibility to stress fracture.

d. By 2004, there was evidence to suggest that bisphosphonates might increase the incidence of stress fractures in a physically fit, highly active, metabolically normal population of Israeli soldiers.

e. Certainly by 2005, after having access to all of the animal data described above, the numerous adverse event reports describing low energy femoral fractures, and the Odvina and Lane reports, Merck should have been fully aware of Fosamax's potential to cause serious fractures of the femoral shaft and at a minimum sought to study this serious problem.

VI. MERCK'S ATTEMPT TO ADD LANGUAGE TO THE FOSAMAX LABEL IN SEPTEMBER OF 2008 MISCHARACTERIZED FOR THE FDA THE TRUE NATURE OF THE AFF PROBLEM

59. On September 15, 2008, Merck submitted to the Food and Drug Administration ("FDA") a proposal to update the labeling for Fosamax to include a description in the Precautions section of the label of "Low-Energy Femoral Shaft Fractures." Specifically, Merck proposed the following language be added:

> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopaedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be

considered, pending evaluation of the patient, based on individual benefit/risk assessment.

60. Along with this proposed labeling, Merck submitted to the FDA adverse event reports, some of which I describe above, reflecting a number of femoral fractures which Merck labeled as "Atypical Femur Fractures." In addition, Merck submitted to the FDA a document entitled "2.5 Clinical Overview," which appears to contain the purported medical and scientific rationale for the proposed label change. I have reviewed what I believe to be Merck's entire submission to the FDA in September 2008. According to the information I have, Merck did not submit anything else to the FDA in support of this proposed label change.

61. It appears that on May 22, 2009, the FDA sent a letter to Merck informing Merck that it could not "approve these applications in their present form." The FDA informed Merck that its "justification for the proposed **PRECAUTIONS** section language is inadequate." The FDA further informed Merck that "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." As I will explain in more detail below, it is not surprising that the FDA made this determination given the inadequate description and justification that Merck provided to the FDA regarding atypical femoral fractures.

62. In 2009 the American Society for Bone and Mineral Research ("ASBMR") convened a Task Force to address the issue of atypical femoral fractures primarily in patients who had been taking bisphosphonates for a long period of time. The Task

Force was asked to review the currently available information to determine what was known and what was not known about atypical femoral fractures and their relationship to BP use, and to recommend a case definition. The Task Force Report was published in the *Journal of Bone and Mineral Research* in 2010 (25:2267–2294.).

63. I, along with a colleague Elizabeth Shane from Columbia University, was selected by the ASBMR to be a co-chairperson of the Task Force. As I discuss above, my work in the field of skeletal fatigue and microcrack-mediated remodeling in bone biomechanical and physiological adaptation makes me particularly suited to marshal the information and resources necessary to adequately understand the issues surrounding atypical femoral fractures.

64. The Task Force Report summarizes what was known at the time about atypical femoral fractures, their relationship to bisphosphonates, and their possible pathogenesis. Table 5 in that report lists 37 published case series and reports on atypical femoral fractures, starting with the initial report by Odvina et al. in 2005. In 2008, 13 of those 37 published case series and reports were available to Merck. By May of 2009, 19 of those 37 were available to Merck. Additionally, the Task Force cited a total of 177 published or available articles and posters. Of those 177, 114 were available in 2008 or earlier and 120 were available before May of 2009.

65. Although the Task Force in 2010 could not conclude that, from a scientific perspective (i.e. very high certainty), bisphosphonate use and atypical femoral fractures were related in a cause and effect

manner, it seemed likely that bisphosphonate use was a substantial factor in causing atypical femoral fractures because (1) more than 90% of cases of AFF occurred in association with BP treatment for osteoporosis, (2) there was no indication of osteoporotic changes in the femurs of this relatively young cohort; indeed the increased cortical thickness that was noted at the time should, from a mechanical standpoint, be associated with increased structural rigidity, not reduced strength, and (3) there were several plausible mechanisms of action which could explain how long-term use of Fosamax and other BPs would lead to an AFF.

A. Merck's September 2008 Submission To The FDA Failed To Demonstrate To The FDA The Potential Underlying Pathogenic Mechanisms Connecting The Long-Term Use Of Fosamax With Insufficiency Stress Fractures.

66. One of the most important aspects to understanding the how and why of AFF is an examination of the possible pathogenesis of this unusual fracture. Indeed, prior to the introduction of Fosamax, subtrochanteric femoral fractures rarely were reported with the clinical criteria associated with AFF.

67. For more than 15 years, I have been examining the relationship between bisphosphonate use and bone material properties. My work, along with dozens of other scientists, shows convincingly that continuous use of Fosamax and other BPs can change important bone characteristics and properties, such as bone toughness. Scientists such as myself have shown that

continuous use of Fosamax and other BPs results in microcrack accumulation, AGE accumulation, increased bone homogeneity, and a greater proportion of older bone, all of which have the effect of decreasing bone toughness, or the bone's ability to withstand repeated low energy forces without breaking.

68. As I discuss above, decreased bone toughness can lead to stress fracture. Additionally, Fosamax and other BPs reduce the body's ability to repair a stress fracture once it has begun, but prior to complete fracture. This might explain why a large number of bisphosphonate-induced stress fractures go on to completion. Indeed, normally a stress fracture will heal itself if the patient simply decreases his/her activity level for a period of time. However, AFFs which begin as stress fractures appear to progress to completion at a much higher rate than would be expected.

69. I have reviewed Merck's September 15, 2008 submission to the FDA, including the "Clinical Overview" document which purports to provide the justification and rationale for the proposed label change. Nowhere in Merck's submission does it provide the FDA with any possible pathogenesis for AFF from long-term Fosamax. By September 15, 2008, there were literally dozens of published scientific articles, including many on which I was an author, which provided evidence for a possible pathogenesis of AFF.

70. An explanation regarding the possible pathogenesis of AFF is particularly important in this context because Fosamax is a drug that was designed

to prevent osteoporotic fractures.[4] Without an adequate explanation to the FDA about why AFFs might be different than other osteoporotic fractures, the FDA and others might conflate the two types of fractures. Importantly, the data suggest that Fosamax may be particularly effective in reducing fractures among women with osteoporosis in the first several years of treatment. By contrast, AFFs generally do not occur until a patient has been taking Fosamax and other bisphosphonates for five years or more (the Task Force Report in 2010 identified the median duration of treatment before fracture as 7 years). Thus, a more detailed presentation to the FDA would have revealed that there is little overlap between the therapeutic use of Fosamax and its harmful side effect of AFFs.

71. By contrast, less than two years later, the Task Force examined the available literature and evidence regarding a possible pathogenesis for AFF and provided the medical community, and the FDA, with a detailed explanation of how long-term use of Fosamax and other BPs could lead to an AFF. This prompted the FDA to take quick action in requiring manufacturers to update the BP labeling with a warning regarding the potential risk for AFF.

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[4] I offer no opinion herein regarding the efficacy of Fosamax in preventing osteoporotic fractures.

B. Merck's September 2008 Submission To The FDA Failed To Explain That AFFs Were Unusual Fractures That Had Rarely Been Reported In The Literature Prior to the Availability of BPs

72. In reviewing the proposed labeling Merck sent to the FDA, as well as the "Clinical Overview" that Merck provided the FDA, Merck repeatedly emphasized that fractures with "similar clinical features" had previously been reported in patients not taking Fosamax. In the "Clinical Overview" document Merck provided to the FDA, Merck stated "[w]hile these fractures are less common than other osteoporotic low-energy fractures (representing about 6% of fractures of the femur), they occur in a similar population of elderly individuals and have been reported prior to the availability of bisphosphonates." Although it is true that stress fractures, including completed stress fractures, had previously been reported in the literature, the nature of AFF is unusual and cannot be identified properly without radiographic evidence. This often was not available prior to the availability of BPs or prior to the identification of AFF as a separate pathololgy, and so the incidence prior to the availability of bisphosphonates was really unknown. Merck's submission to the FDA fails to acknowledge the crucial distinction between subtrochanteric or femoral shaft fractures, and AFF, and improperly implies a rate of non-bisphosphonate exposed AFF that was unknown, and which conflates the occurrence of any subtrochanteric fracture with fractures that have specific features of atypia.

73. As I discuss above, stress fractures have unique clinical characteristics. First, they are often painful in the affected area. Second, they are often imaged on x-ray as having a periosteal or endosteal reaction indicative of the bone's attempt at repair. Third, they appear on x-ray generally as an incomplete transverse fracture. Finally, they occur not from trauma, but from repeated low energy loading of the bone which is unable to be repaired in sufficient time to prevent the stress fracture from occurring.

74. Importantly, even though Merck knew in September of 2008 that AFFs had a relatively unique clinical appearance, Merck made little effort to describe that to the FDA. In fact, my review of the submission by Merck indicated that Merck told the FDA only that the femoral fractures were "low energy," that some patients experienced "prodromal pain," and that some patients had the "imaging features" of a stress fracture. At that point in time, many authors had adequately described AFFs as being low energy, femoral shaft or subtrochanteric fractures, which a transverse fracture line, a periosteal reaction, associated with cortical thickening, prodromal pain, and bilaterality. In fact, in the reports received by Merck in 2006 from Singapore, the doctors there described these unusual fractures in a very similar way: low (or no) energy, subtrochanteric transverse fractures of the shaft, some with bilaterality, and all taking Fosamax. Likewise, in the Neviaser article which was published in March of 2008, the authors described these fractures as "simple, transverse, or short oblique . . . in areas of thickened cortices with a unicortical beak." In fact, although different studies and authors have used slightly different variations on

how they describe AFF, there is, and was before September of 2008, remarkable consistency in the overall description of this unique fracture and its high association in the literature with Fosamax and other bisphosphonates. It was this consistency that allowed the ASBMR Task Force to achieve consensus on the definition for an atypical femoral fracture.

75. It is true that some of the studies which examined AFF identified some individuals with the atypical fracture pattern who had not been taking any BP. About 90% of the patients who had the AFF pattern had previous exposure to BPs. Thus, approximately 10% of those patients had no reported prior exposure to BPs. In the second Task Force Report, the relative risk for an AFF in patients on a BP ranged in different studies from 2.11 to 66.9, with an average adjusted relative risk of 31, suggesting convincingly that BP use increases the risk of sustaining an AFF. The Task Force recognized in its first report that not everyone presenting with an AFF had BP exposure when it stated "[a]lthough atypical femoral fractures have been reported *most prominently* in individuals who have been treated with BPs, such fractures have been reported in individuals with no history of BP exposure." (Italics added). The updated Task Force Report, however, states "Although the task force still holds the opinion that a causal relationship between BPs and AFFs has not been established, evidence for an association has continued to accumulate in the 2 years since the first report was published and is quite robust. Moreover, the fairly consistent magnitude of the association between BPs and AFFs is unlikely to be accounted for by unknown or unmeasured confounders." I believe a statement

such as that accurately conveys the relative frequency with which AFFs had been seen among both exposed and non-exposed individuals.

76. In its submission to the FDA, Merck should have better described this unique fracture to the agency and highlighted that this fracture pattern, particularly in the femoral shaft, was rarely reported prior to the availability of BPs. Instead, Merck appears to have created a submission which suggests that this fracture is much more common in the absence of BPs than it actually is.

C. Merck's September 2008 Submission To The FDA Improperly Attributed Various Risk Factors To AFFs, Including Osteoporosis

77. In its proposed labeling to the FDA, Merck includes the following sentence: "Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g. vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care."

78. In the "Clinical Overview" document submitted by Merck to the FDA, Merck further made these statements: (1) "Stress fractures are seen mainly in postmenopausal *osteoporotic* women and are becoming more common with the increase of elderly population and its increasing involvement in relatively intensive physical/fitness activities."; and (2) "In addition to abnormally decreased bone mineral density (BMD) associated with osteoporosis, long-term

immobilization/disuse, and use of glucocorticoids, the presence of joint deformity, leg-length discrepancies, muscle weakness, and spasm with resulting alteration in force distribution across the joints is likely to be very important in the development of insufficiency fractures." (Italics added).

79. When the Task Force examined the actual data, many of the "risk factors" identified by Merck in its submission to the FDA simply were not associated with AFF. Importantly, the Task Force noticed that many of the patients with this fracture pattern had "normal or low BMD, but not osteoporosis in the hip region." We identified the fracture pattern as being distinct from a typical osteoporotic fracture. This is consistent with my opinion regarding the likely pathogenesis of AFF as unrelated to any underlying BMD deficiency. Moreover, Merck failed to identify increased cortical thickness as a risk factor, although it had been widely discussed as associated with occurrence of AFFs. Identifying this association would have made it more clear to the FDA that AFFs were not the typical fracture associated with osteoporosis, which causes cortical thinning. Further, although the Task Force identified rheumatoid arthritis, glucocorticoid use, and PPI use as being possibly related to the fracture pattern, there is little evidence that the myriad other "risk factors" identified by Merck have anything to do with AFFs (i.e. "leg-length discrepancies" and "muscle weakness").

80. Further, as the co-editor of a book which focused almost exclusively on stress fractures, it is my opinion that Merck improperly suggested to the FDA risk factors for stress fracture (generally) which are not supported by the available data. For example, in the

book on stress fracture for which Dr. Milgrom and I are co-editors, the relationship between Bone Mineral Density ("BMD") and stress fractures was considered to be "equivocal and difficult to interpret." This suggests that osteoporosis, if defined by BMD, has little support in the literature as a causative factor for stress fracture. In another book in which I wrote a chapter about stress fractures, I examined the relationship between BMD and stress fracture and concluded the data do not support "the hypothesis of a close relationship between low bone density and stress fracture . . . ."

81. In my opinion, it appears that Merck was attempting to confound the true nature of the association between Fosamax and AFFs by identifying numerous potential risk factors, very few of which were actually grounded in the available data. It appears that the FDA agreed with this as it stated in its May 22, 2009 letter to Merck that "[d]iscussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting."

D. Merck's September 2008 Submission To The FDA Improperly Conflated The Underlying Fracture Mechanism (Stress Fracture) With The Ultimate Outcome (Completed Subtrochanteric Fractures)

82. In its proposed labeling, Merck stated that "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate treated patients."

Thereafter, however, Merck only identified these fractures as "stress fractures" in its proposed labeling. In the "Clinical Overview" document Merck provided to the FDA, Merck focused much of its discussion in the "Introduction" of the document on stress fractures.

83. I was the co-editor of a book entitled *Musculoskeletal Fatigue and Stress Fractures* (2001), which focused almost exclusively on fatigue-type stress fractures. The fact is that the vast majority of stress fractures never progress to a full and complete fracture. "Stress fractures," in the medical community, commonly refers to an incomplete fracture of a long bone which is clinically diagnosed by pain in the affected region, an x-ray or MRI showing a periosteal or endosteal reaction, and/or a bone scan showing increased local metabolic activity in the painful region. Generally, doctors treat stress fractures in patients by prescribing rest or inactivity in the affected bone. The vast majority of stress fractures heal without any further intervention and do not progress to a complete fracture.

84. By choosing to characterize AFFs as "stress fractures" in its submission to the FDA, Merck improperly conflated the underlying fracture mechanism that leads to AFFs with the ultimate outcome. It is true, as the Task Force has now twice pointed out in its reports, that AFFs are the result of a stress/fatigue type process on the proximal femoral shaft. As I describe in great detail herein, Fosamax and other BPs affect the material properties of bone over time by reducing bone toughness and its ability to repair microcracks. As a result, on the lateral side of the femoral shaft, some women (and men) who have continuously taken Fosamax for several years may

develop a stress lesion. However, Fosamax also prevents the normal repair of those stress lesions, allowing the initial stress fracture lesion to continue to grow until complete fracture of the bone. Even an incomplete AFF is a serious medical condition as many of these patients will require surgical intervention to prevent the eventual complete fracture of the femur. As pointed out by the Task Force, intramedullary rods are the current standard of care in such cases.

85. However, a large percentage of these stress lesions in patients treated with Fosamax and other BPs go on to completion. As the task force noted, AFFs have high morbidity "[b]ecause of the propensity for delayed healing." And because the population of patients who develop AFFs is younger [Shane et al., 2013] and more active, significant lifestyle and workplace limitations are associated with these fractures in a population that might normally still be quite vigorous. Thus, characterizing AFFs as stress fractures in product labeling for Fosamax improperly suggests to medical practitioners that AFFs are much more inconsequential than, in fact, they are.

86. In its May 22, 2009 letter to Merck, the FDA stated that "[i]dentification of 'stress fracture' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." It appears that by conflating the underlying fracture mechanism (stress fracture) with the ultimate outcome (a completed subtrochanteric fracture), Merck gave the FDA the impression that AFF are simply stress fractures. As I discuss, because they often will progress to a complete fracture of the largest bone in the body, they are much more significant than "garden-variety" stress fractures, which usually heal

uneventfully with simple rest and without full fracture.

E. Summary

87. Overall, it appears to me that Merck failed to adequately apprise the FDA of the true nature of the AFF problem in September of 2008 given the data that was available to it at that time. It is difficult to appreciate the significance of this fracture in the context of a medication that is supposed to prevent fractures unless a detailed discussion of a possible underlying pathogenesis is provided. Merck failed to inform the FDA of the relative rarity of this fracture prior to the availability of Fosamax and, instead, simply stated that the fracture was seen in patients not taking a BP. It appears that Merck attempted to confound the underlying possible causes of AFF by identifying numerous "risk factors," many of which were not supported by data, and by failing to report potential risk factors (e.g. increased cortical thickness) that would have suggested that these fractures were not "osteoporotic fractures." Finally, Merck improperly equated AFF with stress fractures conflating the underlying fracture mechanism with its ultimate outcome.

88. By contrast, the Task Force undertook to look at the issue of AFFs in a very detailed and systematic manner. We considered all the available literature, examined a possible pathogenesis for the fracture, developed a case definition to assist practitioners, researchers, regulatory agencies, and manufacturers in identifying the fracture, we recommended future research, and we recommended labeling changes to BP medications. After approaching the issue in this

manner, the FDA acted very swiftly by requiring manufacturers to update bisphosphonate labels to reflect this significant risk.

I declare under penalty of perjury pursuant to the laws of the United States of America that the foregoing is true and correct.

Executed this 29th Day of September, 2013.

s/ David B. Burr
David B. Burr

[Exhibit 3 to Ecklund Declaration]

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (No. II) THIS DOCUMENT RELATES TO: ALL CASES	Civil Action No. 08-08(GEB)(LHG) MDL No. 2243

DECLARATION OF CURT DANIEL FURBERG, M.D., PH.D.

I. INTRODUCTION AND QUALIFICATIONS

I, Curt Daniel Furberg, M.D., Ph.D., hereby declare that all of the following are true, to the best of my personal knowledge and upon information and belief.

1. I am a medical doctor admitted to the practice of medicine in Sweden. I received my medical training and a PhD-equivalent at the University of Umea, Umea, Sweden.

2. From 1974 through 1985, I was employed at the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) in Bethesda, Maryland. For the first nine (9) years at the NIH, I worked in the Clinical Trials Branch and served as its Chief from 1979 to 1985.

3. I received an academic appointment as Professor of Medicine in 1986 from Wake Forest University School of Medicine in Winston-Salem, North Carolina. I was appointed Director, Center for Prevention Research and Biometry and Head, Section of Prevention Research and Biometry in the Department of Medicine. In 1989, the Department of Public Health Sciences was established and I was appointed Chairman. I served in this capacity until 1999. I retired as Professor of Public Health Sciences at Wake Forest School of Medicine as of June 30, 2012. I am currently Professor Emeritus at the school. A copy of my CV is attached as Appendix A.

4. During my 13-year leadership and direction of the Center and the Department, we grew from one to approximately 300 persons. Three Sections were established within the department — Epidemiology, Biostatistics and Social Sciences and Health Policy. We successfully competed for funding from the National Institutes of Health and, in recent years, we have ranked nationally as one of the top two departments of our type (for NIH funding).

5. I have more than three decades of expertise and experience in the areas of epidemiology and clinical trial design, conduct, monitoring, interpretation and reporting. I am considered by my peers to be a national leader in this field. The following are illustrative of my relevant experience and expertise:

   a. I have served as Principal Investigator or Scientific Project Officer on a large number of

primarily cardiovascular clinical trials, having played a very active role in their design, conduct, monitoring, interpretation and reporting. These trials documented the efficacy and safety of various interventions and led to improvements in the quality of care for millions of patients with coronary heart disease, heart failure, hypertension or other vascular conditions. In addition, I served as the Principal Investigator (recipient) of a grant from the Attorney General Consumers and Prescriber Program to develop educational modules for healthcare professionals. Funding for this program, coordinated by the Attorney General's office in Portland, Oregon, came from a large settlement with Pfizer regarding the illegal off-label promotion of the drug Neurontin.

b. I have served or currently serve on the Data Safety Monitoring Committee for over fifty clinical trials, including several trials sponsored by Merck. These committees monitor the efficacy and safety of treatment and prevention trials in progress and are charged with recommending early trial termination, if efficacy is clearly documented or if harmful effects outweigh the benefits. These trials have been sponsored by the National Institutes of Health, Foundations, the pharmaceutical industry and others. Currently, I am on the Data Safety Monitoring Committee of two industry-sponsored trials. Thus, I am very experienced in the generally accepted approaches to weighing favorable and

unfavorable effects of interventions, primarily medications.

c. I have frequently been consulted on clinical trial issues by colleagues at academic institutions and I have conducted trials sponsored by pharmaceutical companies. I consulted for Wyeth as an expert regarding the combination fenfluramine- phenteramine (so-called "fen-phen") in determining the magnitude of the adverse effects associated with its use. I have also interacted with the World Health Organization.

d. I have also been retained as an expert witness for patients who claim that they have suffered harmful drug effects and for pharmaceutical companies defending themselves against such claims. I served as an expert on behalf of Wyeth in a case against a woman who claimed that her hormone replacement therapy had caused her stroke. I have also been retained as an expert for a pharmaceutical company involving litigation regarding a prescription drug in Canada.

6. In addition, I am a past charter member of the U.S. FDA Drug Safety and Risk Management (DSRM) Advisory Committee. This Committee was established by the FDA to provide expert advice on drug safety issues. My term ended in May, 2006. It was as a member of the DSRM Committee that I participated in the FDA Hearing on COX-2 inhibitors in February, 2005. I have been invited as an expert to serve on FDA hearings in 2007, 2008, 2009, and 2010.

7. In collaboration with four other Committee members, we reported our views about the FDA and drug safety in a recent article entitled "The FDA and Drug Safety: A Proposal for Sweeping Changes" (*Arch Intern Med* 2006;166:1938–42).
8. I have served as chair of the Outpatient Prescription Drug Subcommittee and as a member of the Medical Center's Formulary Committee. I was recently invited to be a member of the United States Medicare Evidence Development & Coverage Advisory Committee. I have also served on the State of North Carolina Drug Utilization Review for Medicaid.
9. As an expert on drug safety, I have testified twice at Congressional Hearings. I was invited in March, 2005 to provide a written testimony for the U.S. Senate Committee on Health, Education, Labor and Pensions regarding how well the pharmaceutical industry pursues safety signals and disseminates safety information to the medical community and to consumers. I also provided live testimony in March, 2007 for the U.S. House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations regarding the pharmaceutical companies' oversight of drug safety, including applicable laws, regulations and the consequences associated with violations thereof.
10. I am the past Chair of the Steering Committee of the Cardiovascular Health Study sponsored by the National Heart, Lung, and Blood Institute. This very large epidemiologic study was initiated approximately twenty-five years ago to investigate

risk factors (predictors) for coronary heart disease and stroke in people 65 years of age or older. I am also past Steering Committee Chair of the Ginkgo Evaluation of Memory Study sponsored by the National Center for Complementary and Alternative Medicine of the National Institutes of Health.

11. I was recently invited to be a member of the Advisory Board of the British Medical Journal, one of the leading medical journals in the world.

12. I served as the Research Subject Advocate Advisor and as a member of the General Clinical Research Center's Human Subject Protection Committee, which monitored high- risk studies conducted at Wake Forest University School of Medicine. My role was to help protect the safety and well-being of study participants by overseeing and monitoring ongoing trials for possible adverse treatment effects. As a result of my work, we promptly facilitated the termination of two local VIOXX trials soon after the drug was taken off the market. I am also Past Chair of an institutional Data Safety Monitoring Committee at Wake Forest.

13. As referenced previously, I have authored numerous publications on the subject of clinical trials. Along with two colleagues from the National Institutes of Health, I co-authored a text book entitled *Fundamentals of Clinical Trials*. The 4th Edition was published in 2010 and we are currently working on the 5th Edition. This is considered a leading text and is used widely for teaching and as a reference for clinical trial researchers. A more recent text is entitled "*Data Monitoring in Clinical*

Trials - A Case Studies Approach," Springer 2006. All 29 cases reviewed in this text address issues of benefit, harm and benefit-to-harm balance. Another text entitled "*Evaluating Clinical Research — All that Glitters is not Gold*," Springer 2007, summarizes many of the clinical trial lessons I have learned over more than three decades. It contains many examples of violations of fundamental principles of medical research. I also have written a book for patients entitled "*Knowing Your Medications – A Guide to Becoming an Informed Patient*". These publication I co-wrote received sponsorships from Merck.

14. I am also the author or co-author of more than four hundred (400) peer-reviewed articles and sixty (60) book chapters on various topics, chiefly including epidemiology and clinical trials. More than seventy (70) of the publications deal with drug safety. In several of them, Merck appointed me to serve on Data Safety Monitoring Committees; in some of them, I was appointed and served as the Chair of the Data Safety Monitoring Committee.

15. Since 1983, I have served on sixteen editorial boards. I am currently a member of the editorial board of one professional journal – *Trials* (dealing with the main subject of clinical trials).

16. I have received the following awards:

    1983 – *Director's Award* from the National Institutes of Health

    1998 – *Women's Health Initiative Achievement Award*, NHLBI

    2001 – *Established Investigator in Clinical Science Award* from Wake Forest University

2002 – *Ancel Keys Lecture Award*, American Heart Association

2004 – *Joseph Stokes III Award*, American Society of Preventive Cardiology

2004 – Honorary degree *Doctor Honoris Causa* from Umea University

2004 – *Rockefeller Foundation Residency Award*, Bellagio, Italy.

2005 – Elected *Fellow of the Society for Clinical Trials*.

2007 – *Health Care Heroes - Lifetime Achievement Award* from the Business Journal

2011 – *Wake Forest School of Medicine Team Science Award.*

2013 – *Wake Forest School of Medicine Team Science Award*

2013 – *Bruce Squires Award*, awarded annually to the authors of the research paper published in the Canadian Medical Association Journal that "was most relevant to the practice of medicine and most likely to impact it in a positive way."

17. I have served as an expert witness in Fosamax litigation for several years on the topics of clinical trials, pharmaceutical efficacy, and pharmacovigilance. My rate of compensation is $500/hour. After extensive *Daubert* hearings and briefing, I was recognized by the presiding District Judge in *In re Fosamax Products Liability Litigation*, MDL No. 1789 (S.D.N.Y.) (Keenan, J., presiding), as an expert competent with sufficient bases and methodology to testify in these areas

(clinical trials, pharmaceutical efficacy, and pharmacovigilance). Further, my opinions on clinical trials and efficacy have been cited by the Fosamax MDL 1789 District Court in published rulings pertaining to Fosamax's lack of efficacy for certain populations of patients. *In re Fosamax Prods. Liab. Litig.*, 742 F.Supp.2d 460, 468–73 (S.D.N.Y. 2010) (citing my testimony about the lack of efficacy for osteopenic patients in affirming the jury's finding that Fosamax was unreasonably dangerous and therefore defectively designed). In an earlier opinion in the same case, after citing my testimony and the testimony of regulatory expert, Dr. Suzanne Parisian, the *Fosamax Products Liability Litigation* MDL Presiding Judge ruled:

> Even if the jury finds that Merck has the benefit of a rebuttable presumption by way of Fosamax's FDA approval, based on this evidence, the jury may reasonably conclude that the risks of Fosamax outweigh its benefits when used for the prevention of osteoporosis by those with a T-score better than -2.5.

In re Fosamax Products Liab. Litig., 2010 WL 1257299, *6 (S.D.N.Y. 2010)

II. ASSIGNMENT AND SUMMARY OF OPINIONS

A. Assignment:

18. As referenced above, I previously have provided the opinions in this Declaration through my trial and deposition testimony in *In re Fosamax Products Liab. Litig.*, MDL No. 1789. For this Declaration, I have been asked to provide my opinions related to

the extent of the proven fracture reduction efficacy of Fosamax as to non-osteoporotic patients and the duration of proven fracture reduction efficacy for osteoporotic patients.

19. In conjunction with the assignment, this expert report includes my opinions regarding the Sponsor's actions related to a) adherence to established standards for the conduct of research, b) dissemination of trial results and c) obligations to inform and warn practicing physicians, research subjects and regular patients.

B. Bases for Opinions:

20. The bases of my opinions derive, in part, from my education, training, experience, research and what is accepted within the community of physicians, scientists and public health professionals who are knowledgeable in the proper conduct and reporting of clinical trials and in the proper dissemination of drug safety information to clinicians and to patients. I have also based my opinions on the review of various clinical studies and materials, many of which are exhibits to my expert report and others which are included in a list attached (Appendix B). My opinions (discussed below) may be further refined, subject to ongoing medical and scientific study and the continuing review of additional information produced from this litigation.

21. I am uniquely qualified to render these opinions, based on my extensive experience in drug evaluation and all aspects of clinical trial methodology and based on my knowledge of regulations, including drug safety and labeling.

C. Summary of Opinions:

22. The following is a brief summary of my opinions:

a. The Sponsor's clinical trials for Fosamax fail to establish that Fosamax is effective in reducing the risk of fracture of any patient who does not have osteoporosis defined either by a femoral neck T-score of -2.5SD or less or a prior vertebral fracture. For osteopenic patients who do not have osteoporosis (defined as a femoral neck T-score of -2.5SD or less or a prior vertebral fracture at baseline), there is no proven fracture reduction benefit conferred through the use of Fosamax. For those patients, any risk of harm would outweigh Fosamax's benefits.

b. Even for osteoporotic patients, the Sponsor's clinical trials for Fosamax fail to establish that Fosamax is effective in reduction the risk of fracture beyond three years of use. For osteoporotic patients, there is no proven fracture reduction benefit after three years of Fosamax use and any risk of harm would outweigh Fosamax's benefits.

III. THE ROLE AND CONDUCT OF CLINICAL TRIALS

23. For regulatory approval of prescription drugs in the United States of America, a drug sponsor is required to conduct clinical trials. A clinical trial is a prospective study comparing the effect and value of a particular intervention against a control in human being. Clinical "studies" differ from clinical "trials" as clinical studies are uncontrolled

whereas a true clinical trial must have a control group.

24. There are several phases of studies which are divided into three phases before the FDA grants New Drug Approval ("NDA"). "Preclinical" studies are conducted in animals, typically, before any human testing is conduct.

    a. Phase I studies are conducted in a small number of humans in order to determine basic information about the drug such as drug tolerance, metabolism, bioavailability, interaction, pharmacokinetics, and pharmacodynamics.

    b. Phase II studies sometimes are conducted as controlled clinical studies with an intervention group and a control group. Phase II studies or trials are therapeutic exploratory studies, looking to establish dose ranges and obtain basic biologic response information, typically through biomarkers. Compared to a Phase III trial, Phase II trials are typically much smaller and of shorter duration and are directed to the initial evaluation of the drug's effectiveness for a particular indication in patients with a disease or condition. Information obtained from Phase II trials are used to then design the Phase III trial or trials.

    c. If the Phase II trials suggest effectiveness, Phase III trials are then conducted in a much larger group of patients and for a longer period of time. Phase III trials are the final phase of clinical trials before an NDA is granted by the FDA. Phase III trials evaluate pre-specified

endpoints in a double-blind methodology. Double-blinding is important because neither the subjects of the study (the patients) nor the person conducting the experiment know whether the patient is receiving the control or the intervention.

d. Phase IV trials are conducted after a drug is on the market and are therapeutic use studies which examine the drug in broad or special populations and seek to identify uncommon adverse events.

25. In the conduct of a clinical trial, each patient in the trial must be followed from a well defined point in time which is referred to as "time zero" or, more frequently, "baseline". In the context of a clinical trial, the term "baseline" typically refers to the starting point of the data collection: i.e., when you actually begin administering an intervention or control to a patient and what that patient's status was at that moment in time. For instance, if you refer to an objective baseline set of entry data (such as a patient's weight, for example), you can measure the change in those data during the conduct of the clinical trial.

26. Clinical trials have three major limitations regarding the discovery or elucidation of risks associated with a drug: 1. The trial may not be large enough to detect a rarely occurring adverse event; 2. An adverse may take a long period of time to develop and clinically manifest and the typical manifestation may post-date the trial's study period; 3. Clinical trials typically are not designed to specifically look for unexpected adverse events.

Therefore, there is an adage about adverse events and clinical trials: "The absence of reports does not mean the absence of events."

IV. FOSAMAX HAS LIMITED FRACTURE REDUCTION EFFICACY.

27. The disease for which Merck first proposed the use of Fosamax as an intervention is "osteoporosis". Before 1994, the disease "osteoporosis" was primarily a clinical diagnosis made by clinicians without reference to specified criteria. In 1994, the World Health Organization promulgated a standardized system for the diagnosis of osteoporosis through the measurement of bone mineral density via Dual Energy X-ray Absorptiometry ("DXA") machines. The WHO system referenced the system of comparison between a particular patient's bone mineral density ("BMD") and the reference point which was the average for a healthy thirty year-old white female. Any difference from the patient's score and reference point is referred to via the quantification of the standard deviation, also referred to as the T-score. The reference point on the T-score chart is 0. The further into the negative the particular patient's T-score is, the less bone mineral density the patient has. The WHO system established -2.5 standard deviations as the numerical cut-off for the BMD-based diagnosis of osteoporosis.

28. Under the WHO system, patients with T-scores between -1.0 and -2.5 standard deviations are referred to as osteopenic patients. Osteopenia

itself is not a disease. Osteopenia is simply a way of describing low normal bone mineral density.[1]

29. Osteoporosis, while called a disease, is not itself a disabling condition. Rather, it is the fractures associated with osteoporosis that physicians hope to prevent by prescribing interventions such as Fosamax.

30. Most post-menopausal women are neither osteopenic nor osteoporotic. According to the Merck-sponsored National Osteoporosis Risk Assessment Study, 39.6% of postmenopausal women have osteopenia while only 7.2% have osteoporosis.[2] According to NORA, then, in the postmenopausal women population there are 5.5 times more osteopenic women than osteoporotic women.

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[1] World Health Organization. Assessment of Osteoporotic Fracture Risk and Its Role in Screening for Postmenopausal Osteoporosis. WHO Technical Report series no. 843. Geneva: World Health Organization, 1994. As Merck's Director of Clinical Research for Fosamax, Dr. Arthur Santora, testified in a deposition taken in *In re Fosamax Products Liability Litigation* (MDL No. 1789):

> Q: We're talking about osteopenia, but just to be fair, osteopenia is not a disease, is it?
> A: Osteopenia is just a way of describing low/normal bone density.
> Q: Osteopenia is not a disease, is it?
> A: No, it's not a disease.

(Santora MDL 1789 deposition, p. 332.)

[2] Siris ES, Miller PD, et al. Identification and Fracture Outcomes of Undiagnosed Low Bone Mineral Density in Postmenopausal Women: Results from the National Osteoporosis Risk Assessment. *JAMA* 2001; 286:2815–2822.

31. Fosamax (alendronate) is a member of a class of drugs called bisphosphonates that are approved for use in the treatment and prevention of osteoporosis in postmenopausal women; treatment to increase bone mass in men with osteoporosis; treatment of glucocorticoid-induced osteoporosis and treatment of Paget's disease of bone. It contains a nitrogen atom and, thus, belongs to the N-containing bisphosphonate subclass. Other members of this sub-subclass are Aredia (pamidronate), Boniva (ibandronate) and Actonel (risedronate). Fosamax has a remarkably long half-life in bone of more than 10 years, which may have long-term health consequences.

32. Fosamax was approved by the FDA in 1995 for the main indication of treatment of osteoporosis in postmenopausal women. The indication was expanded to the "prevention of osteoporosis" in 1997, again in postmenopausal women. Importantly, the FDA conferred the approval of these two separate indications before Merck had received the full results from its pivotal Phase III trial series, the Fracture Intervention Trial ("FIT"). Remarkably, neither Merck nor the FDA had FIT's complete data on the fracture reduction effects of Fosamax when compared to the control group at the time the treatment and prevention indications were approved in 1995 and 1997. As a result of the indications received by Merck in 1995 and 1997, millions of non-osteoporotic women have been prescribed Fosamax even though there is no proven fracture reduction benefit for that group of patients.

33. The FIT trial program was the pivotal clinical trial series for the Fosamax Phase III program.

34. Through its very broad clinical trial program for Fosamax, Merck has studied osteopenic and osteoporotic post-menopausal women. Based upon my review of Merck's clinical trials for Fosamax, there is evidence of a fracture reduction benefit for only a specific population and only for a specific period of time. The specific population for which Merck has shown a fracture reduction benefit is for patients who have osteoporosis defined by either (1) a baseline T-score of -2.5SD or worse or (2) a baseline, preexisting vertebral fracture. Merck has studied but did not find any fracture reduction benefit for post-menopausal women who did not have either of these two conditions. Further, for those women for whom a fracture-reduction benefit is conferred, the benefit is time-limited and no fracture reduction benefit has been proven by Merck after thirty-six month window of use.

35. Where clinical trial evidence demonstrates a time-limited benefit for a specific subgroup it is inappropriate to extend by inference or extrapolation that benefit to patients outside that subgroup, particularly when the trial Sponsor is in possession of data indicating that the patients outside the subgroup achieve no benefit from the use of the studied intervention, Fosamax.

36. After Merck received for Fosamax both the treatment indication (in 1995), and the prevention indication (in 1997), Merck received and analyzed the fracture reduction data from its FIT program. In 1998, Merck co-authored and published in the

Journal of the American Medical Association titled "Effect of Alendronate on Risk of Fracture in Women with Low Bone Density but Without Vertebral Fractures: Results from the Fracture Intervention Trial", for which the lead author was Steven R. Cummings, M.D.[3] (Hereafter FIT-Cummings). Several Merck employees co-authored this publication including Desmond Thompson, Ph.D., Thomas A. Musliner, M.D., and A. John Yates, M.D.

37. In FIT-Cummings, patients with a femoral neck T-score of -1.6SD or worse were recruited and studied.[4] The patients were divided into "tertiles". "Tertile" means one-third. The patients in FIT-Cummings were divided into thirds, or tertiles, based upon the severity of femoral neck bone mineral density deficits. Importantly, this tertile analysis was pre-specified in the clinical trial protocol and was conducted before unblinding. (FIT-Cummings, p. 2080.)

38. In the FIT study, there was no benefit in the reduction for clinical fractures for the overall trial population. It is only when one starts cutting up

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[3] Cummings SR, Black DM, et al. Effect of Alendronate on Risk of Fracture in Women With Low Bone Density but Without Vertebral Fractures: Results from the Fracture Intervention Trial. *JAMA* 1998; 280:2077–2082.

[4] Initially, the threshold T-score for FIT-Cummings was -2.0SD or worse. After the trial began, however, results from the Third National Health and Nutritional Examination Survey ("NHANES III") indicated that the FIT inclusion criteria corresponded to 1.6SD or more below the normal adult mean, rather than 2.0SD or more below the normal adult mean (FIT-Cummings, p. 2078.)

the data of the study into tertiles is a benefit seen, and that benefit is exclusively limited to those women in the top tertile: i.e., those women with a baseline femoral neck T-score of -2.5SD or worse. The demonstrated benefit for that group, however, dissipated after thirty-six months of use.

39. The FIT-Cummings tertile analysis is presented at Table 3 of the publication. In analyzing this clinical trial evidence, the acronym "RH" stands for "Relative Hazard". When analyzing "Relative Hazards", scientists use a statistical approach known as the "CI" or "Confidence Interval" to determine whether any difference in hazard risk is "statistically significant". The CI is a key issue in the interpretation of clinical trial findings. For an RH result to be "statistically significant", the CI range must not include the number 1.0. If the CI crosses 1.0, then the results, statistically, may be due to chance.

40. The FIT-Cummings tertile analysis shows that the only group that had a statistically significant reduction in the rate of hazard for clinical fractures was those patients who had a baseline femoral neck T-score of -2.5SD or worse. As the tertiles "improve" into the osteopenic range (i.e., better than -2.5SD), Fosamax was not shown to reduce the risk of fractures. For instance, among women in the middle tertile who had a baseline femoral neck T-score of -2.0 to -2.5SD, more women in the Fosamax group had a clinical fracture when compared to those in the placebo group. There is no numerical evidence of any clinical fracture reduction benefit whatsoever for this tertile of women. Further, when comparing the non-clinical

vertebral fractures, the CI crosses 1.0 (1.04) and, thus, no statistically significant benefit is seen for the non-clinical fractures in the middle tertile. In the bottom tertile (the group of women who had a baseline femoral neck T-score of -1.6 to -2.0SD), there were seven more fractures in the Fosamax group than in the placebo group. There is no evidence of any fracture reduction benefit whatsoever for this tertile of women. Further, when comparing the non-clinical vertebral fractures, the CI crosses 1.0 (2.07) and, thus, no statistically significant benefit is seen for the non-clinical fractures in the bottom tertile.

41. In an attempt to broaden the beneficial findings of the FIT trial, the FIT-Cummings authors engaged in a post-hoc analysis. Post-hoc analyses are analyses that are not pre-specified in the clinical trial protocol and usually are conducted after unblinding. Because they are not pre-specified and are done post-hoc after unblinding, post-hoc analyses are scientifically suspect because of the risk of profound bias that can invade the analysis. Post hoc analyses are not accepted by the FDA or the medical community as conclusive.

42. However, even in the FIT-Cummings post hoc analyses, the authors were unable to find a meaningful fracture reduction benefit for those patients with T-scores better than -2.5SD: "In post hoc analyses, alendronate reduced the risk of hip fractures by 56% among women with a femoral neck T-score of -2.5 or less ... There was no reduction in risk among those who femoral neck T-scores were more than -2.5[.]" (FIT-Cummings, p. 2081.) Further: "Alendronate reduced the risk of

clinical fractures by 36% . . . in women whose initial femoral neck T score was -2.5 or less. However, 4 years of alendronate did not significantly affect risk of clinical fracture in those with higher BMD." (FIT-Cummings, p. 2080.)

43. In the same paragraph, however, the authors write: "We observed a 22% lower risk of clinical fractures in those who T-scores were more than 2.0SDs below the normal mean. . . . Alendronate did not decrease the risk of fracture among subjects whose initial T-scores were greater than -2.5." (FIT-Cummings, pp. 2080–81.) These two contradictory sentences about the post-hoc analyses require examination. The only way Merck got to the 22% risk reduction figure was to take one of the two tertiles for which there clearly was no fracture reduction benefit demonstrated (the middle tertile), leave out the other tertile for which there clearly was no fracture reduction benefit demonstrated (the bottom tertile), then average the middle tertile with the top tertile for which there was a fracture reduction benefit demonstrated to come up with a "new score" for 2 of the 3 tertiles. This is analogous to taking one high school class that got an "A" on a standardized exam, grouping it together with another high school class that got an "F" on the exam, and then proclaiming that everyone passes since the average grade is now a "C". Indeed, when one analyzes all three tertiles of the FIT-Cummings study group, the trial fails to demonstrate a statistically benefit for the entire cohort studied. It is not scientifically valid for Merck to pick and choose — on a post hoc, unblinded basis — which groups it will select for

this combined analysis. The trial fails to demonstrate a benefit for the entire study population. It is only by the tertile analysis that any benefit for any pre-specified subgroup is shown: i.e., that group with a baseline femoral neck T-score of -2.5SD or worse.

44. Thus, the only fracture reduction benefit demonstrated in FIT-Cummings is in the top tertile of patients: those who have a baseline femoral neck T-score of -2.5SD or worse. Even for that group of patients, however, the benefit conferred is not infinite in duration of the benefit. The FIT-Cummings article includes, at Figure 3, a "Life Table Graph". The purpose of a "Life Table Graph" is to show the reader when during treatment a benefit first appeared in the trial, and whether and for how long the benefit of intervention was sustained. Because a "Life Table Graph" shows the cumulative number of events, in order to demonstrate a continuing treatment benefit between the control group and the intervention group, the two lines on the graph should continue to diverge. At the point in time when they stop separating, the benefit of intervention has also stopped. At Figure 3 of FIT-Cummings, one can clearly see a divergence of the "Alendronate Sodium" line and the "Placebo" line starting at approximately 18 months of treatment and continuing through approximately 36 months of treatment. At that point, the lines begin narrowing through the remainder of the studied period, showing no continuing fracture reduction benefit after approximately 36 months of treatment.

45. At about the same time as the publication of FIT-Cummings, an FDA biostatistical reviewer named Dr. Anthony Mucci reviewed the FIT results. I received this document from the Plaintiffs Steering Committee for *In re Fosamax Products Liability Litigation*, MDL No. 1789, which I understand received the document through a Freedom of Information Act request to the United States Food & Drug Administration, and which certified the record as an official record from the FDA. The FDA's certification reads: "The following attached document is a true copy of an official record of the United States Food and Drug Administration: 'Statistical review and evaluation, clinical studies, NDA number 20-560 SE8-15, Sponsor: Merck, drug: Fosamax (Alendronate), dated September 4, 1998 by A.G. Mucci, Ph.D:, Statistical Reviewer." (MDL 1789 PSC Exh. 1.0097A.)

46. In his review of the FIT trials' clinical fracture reduction benefits conferred, Dr. Mucci writes: "The performance of Fosamax is especially bad in the restricted nonosteoporotic cohort G, where P equals .22 and where both the relative risk and the difference in cumulative incidences actually favor placebo." (MDL 1789 PSC Exh. 1.0097A, p. 439.) Dr. Mucci also writes: "The clinical fracture trial does not quite attain its primary efficacy goal of a statistically significant decrease in clinical fractures for Fosamax versus placebo unless the patient population is reduced to the osteoporotic cohort." (MDL 1789 PSC Exh. 1.0097A, p. 452.) Dr. Mucci continues: "Furthermore, the nonosteoporotic cohort reveals no efficacy for Fosamax for any category of fracture." (MDL 1789

PSC Exh. 1.0097A, p. 452.) Finally, Dr. Mucci concludes: "Thus, Fosamax can be said to be effective in osteoporotic patients with no prevalent vertebral fracture only if osteoporosis is defined in the more stringent fashion wherein the previous inclusionary criterion, with BMD set at a negative 2 T score, is replaced by a new inclusionary criterion, which sets BMD at a negative 2.5 T score." (MDL 1789 PSC Exh. 1.0097A, p. 452.) This correlates very well with the tertile analysis in FIT-Cummings, which clearly demonstrates the only fracture reduction benefit is for that subgroup of patients with a baseline femoral neck T-score of -2.5SD or worse.

47. In analyzing the 54 months of fracture reduction data from the FIT clinical fracture studies, Dr. Mucci further concludes: "The reviewer's interpretation of these results is: 1. Fosamax provides no advantage over placebo in either the first 18 months or the last 18 months; 2. Fosamax does provide protection against fracture in the middle eighteen months." (MDL 1789 PSC Exh. 1.0097A, p. 451.) This analysis is very consistent with the Life Table Graph results presented at Figure 3 of FIT-Cummings, as well as my opinion that Fosamax has no fracture reduction benefit for any subgroup after thirty-six months of use. Dr. Mucci further concludes: "This analysis should cast some doubt on the value of extended use of Fosamax in patients with low BMD but without prevalent vertebral fractures at start of treatment, who, after three years of subsequent treatment, have experienced no fractures." (MDL 1789 PSC Exh. 1.0097A, p. 451.)

48. In litigation, Merck has attempted to answer these studies' shortcomings through other publications on its clinical trials but none of these studies demonstrates that Fosamax has a fracture reduction benefit for post-menopausal women unless they have either a prior vertebral fracture or a T-score of -2.5SD at baseline.

49. These studies frequently cited by Merck include a 1996 publication in *Lancet* titled "Randomized Trial of Effect of Alendronate on Risk of Fracture in Women with Existing Vertebral Fracture", lead author Dennis M. Black, Ph.D (hereafter FIT-Black)[5]. As the title of the FIT-Black publication shows, however, this portion of the FIT program was limited only to that group of patients with a history of vertebral fracture at baseline: i.e., a subgroup of the population at a very high risk for osteoporotic fracture. (FIT-Black, p. 1540.) This portion of the FIT project was not directed to studying patients without a vertebral fracture at baseline and no fracture reduction efficacy can be inferred to the much larger population of post-menopausal women without a prevalent vertebral fracture.

50. Just as with the FIT-Black study, the earlier publication by Liberman, et al., did not pertain to non-osteoporotic patients.[6] The Liberman study

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[5] Black DM, Cummings SR, et al. Randomised Trial of Effect of Alendronate on Risk of Fracture in Women With Existing Vertebral Fracture. *Lancet* 1996; 348:1535–1541.

[6] Liberman UA, Weiss SR, et al. Effect of Oral Alendronate on Bone Mineral Density and the Incidence of Fractures in Postmenopausal Osteoporosis. *NEJM* 1995; 333:1437–1443.

pertained only to patients who had a baseline vertebral T-score of -2.5SD or worse, with or without prevalent vertebral fracture at baseline. (Liberman, et al., p. 1438.) This trial is not directed to studying patients with a non-osteoporotic T-score. Further, the overwhelming majority of new vertebral fractures recorded during the study period occurred in those patients who had a prevalent vertebral fracture at baseline. (Liberman, et al., p.1441.)

51. Because their pre-specified clinical trial results did not demonstrate a fracture reduction benefit for non-osteoporotic patients, Merck sponsored a post hoc data pooling analysis through which it attempted to present some evidence of Fosamax fracture reduction benefit for non-osteoporotic patients. In the post-hoc analysis by Quandt, et al.[7], the study authors, including several from Merck, pooled data from across the FIT program and attempted to divine a vertebral fracture reduction benefit from Fosamax use for patients who had baseline femoral neck T-scores better than -2.5SD. The reviewers pooled the data for patients who had a vertebral fracture at baseline with those who did not have a vertebral fracture at baseline and concluded that there was an overall vertebral fracture reduction benefit. However, when the data are examined appropriately, one can readily see, in both Tables 2 and 3 of the study, that the CI

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[7] Quandt SA, Thompson DE, et al. Effect of Alendronate on Vertebral Fracture Risk in Women With Bone Mineral Density T Scores of -1.6 to -2.5 at the Femoral Neck: The Fracture Intervention Trial. *Mayo Clin Proc* 2005; 80:343–349.

crosses 1.0 for those patients who did not have a prevalent vertebral fracture at baseline. Therefore, there is no statistically significant difference demonstrated, even in this unblinded post-hoc analysis, in vertebral fracture risk for those women who had a femoral neck T-score of -1.6 to -2.5SD but no prevalent vertebral fracture at baseline.

52. Further, at least two Merck officials who are intimately familiar with the Fosamax clinical trial programs have testified that Fosamax has no evidence of fracture risk reduction for women who are not osteoporotic: Dr. Arthur Santora and Dr. Daniel Baran.

53. In my several years as a testifying expert in MDL No. 1789, I have reviewed several depositions key Merck employees taken in that litigation including Dr. Arthur Santora and Dr. Daniel Baran. I understand from Dr. Santora's deposition that he has served as Merck's Director of Clinical Research for Fosamax since 1989. (Santora MDL 1789 depo., pp.14–15.) Dr. Santora served as the head of the clinical development program for Fosamax and was Merck's physician responsible for the Fosamax Phase III clinical trials. (Goldberg MDL 1789 depo., pp. 22–2; 119–121.)

54. Dr. Santora testified that in the Fracture Intervention Trial, "only those who had osteoporosis, defined by a low bone mineral density at the femoral neck, were found to have a significant risk reduction of all clinical fractures." (Santora MDL 1789 depo., p. 709.) Just as I have observed, and Dr. Mucci has observed, Dr. Santora

testified that, when all non-osteoporotic patients studied were combined with the patients with osteoporosis, there was no statistically significant difference found between the placebo arm and the treatment arm in the trial. (Santora MDL 1789 depo., pp. 708–709.)

55. As presented above, Dr. Santora testified that the Non-Osteoporotic Cohort in the FIT included those patients with a baseline T-score better than -2.5SD. (Santora MDL 1789 depo., p. 720.)

56. Regarding the totality of Merck's clinical trial evidence for Fosamax, Dr. Santora explained the following:

Q: It's my understanding, based on the clinical trial evidence that Merck had and presented to the FDA, Merck cannot say that for those patients without osteoporosis that the use of Fosamax prevents fractures, right?

...

Q: Is that right?

A: Merck has stated that the drug works to reduce the risk of fracture in people who have osteoporosis defined as either vertebral fracture or defined as a low bone mineral density. Your question, I think, is related to whether we have promoted or stated the drug works in other populations to reduce the risk of fracture. The answer is no, we have not indicated that Fosamax reduces the risk of fracture in women who don't have osteoporosis.

Q: Because there's no evidence that it does, right?

A: Right. There's no evidence that any drug reduces the risk of fracture in people who don't have osteoporosis.

(Santora MDL 1789 depo., pp. 795–796.)

57. I agree with Dr. Santora's testimony that there is no evidence that Fosamax reduces the risk of fracture in non-osteoporotic patient. Dr. Santora, however, incorrectly testified that Merck does not attempt to indicate that Fosamax reduces the risk of fracture in non-osteoporotic patient as Merck's Fosamax prevention indication language from the Fosamax package insert expressly tells the prescriber that Fosamax can be used for non-osteoporotic patient to "reduce the risk of future fracture".

58. Dr. Santora is not the only Merck official to testify that Fosamax has no evidence of fracture reduction efficacy for non-osteoporotic patients. Dr. Daniel Baran served as Merck's National Science Director for Osteoporosis from 2003 to 2006, and later served as Merck's Senior Regional Medical Director. (Baran MDL 1789 depo., pp. 123–124, 140–141.) As to Fosamax, Dr. Baran testified: "There is—there are no studies showing that treatment of individuals with osteopenia without a prevalent vertebral fracture reduces the risk of fractures, that is correct." (Baran MDL 1789 depo., pp. 320–321.)

59. The FDA has been concerned for a good period of time about the use of Fosamax in the non-osteoporotic population.

60. The FDA also has been concerned about long-term use of Fosamax. The FDA convened a September

9, 2011, Joint Meeting of the Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee pertaining to the long-term use of bisphosphonates, including Fosamax, several FDA officials testified about the lack of fracture reduction benefit for Fosamax after three years of use. FDA Medical Reviewer Dr. Marcea Whitaker testified that there was a plateau in overall fracture reduction benefit after three to four years of use and that "therapy can be safely discontinued without loss of efficacy." (FDAAC 09/09/11 transcript, p. 27.) Further, FDA Clinical Team Leader Dr. Theresa Kehoe testified that even high risk patients do not benefit with continued Fosamax therapy. (FDAAC 09/09/11 transcript, pp. 76–77.)

61. Further, testifying on behalf of Merck, Dr. Santora testified about Fosamax: "These days you wouldn't treat somebody for osteoporosis if their BMD T-score was -1.6." (FDAAC 09/09/11 transcript, p. 59.)

62. Through FDA Clinical Team Leader, Dr. Theresa Kehoe, and in response to a question from an Advisory Committee member, the FDA has indicated the Fosamax prevention indication is outdated and is being "revisited" by the FDA:

> CLIFF ROSEN: So I guess my question though is when we talk about prevention of osteoporosis you commonly hear people say that an indication for using these drugs is osteopenia. Is that correct or incorrect?
>
> THERESA KEHOE: I would imagine that's technically correct, but I think that

unfortunately the indications have preceded where the standard of is [sic] in the field now, which is that a prevention indication I think is really being revisited all the way around, including by FDA.

CLIFF ROSEN: It's — that's what I wanted to hear, if somebody's looking at this.

THERESA KEHOE: Well I think that might be a topic for later advisory committee, but certainly it's something we're struggling with and dealing with.

(FDAAC 09/09/11 transcript, pp. 86–87.)

63. On June 16, 2013, the FDA sent to Merck a letter titled "INFORMATION REQUEST", indicating as follows: "Given the concerns regarding the long-term safety of bisphosphonates, the Division is considering whether the broad 'prevention of postmenopausal osteoporosis' indication for bisphosphonates is warranted. We would like to hear your perspective on whether there is still utility for a prevention indication for your products. If you believe a prevention indication is still appropriate, address whether the language of the indication should be modified to better define an appropriate target population." (06/16/13 FDA "INFORMATION REQUEST" to Merck Sharpe & Dohme Corp., attn: Elinor Chen, Ph.D., signed by Hylton V. Joffe, M.D., M.M.Sc., Director, Division of Bone, Reproductive, and Urologic Products, FDA.)

V. **CONCLUSION**.

64. Compared to the broad population of post-menopausal women who have actually taken

Fosamax, there exists only a small subgroup of patients for whom there is evidence of a fracture reduction benefit: patients with osteoporosis defined by either a femoral T-score of -2.5SD or worse or by a preexisting vertebral fracture. There is no documented clinical trial evidence of a fracture reduction benefit for the rest of the population of post-menopausal women who have used Fosamax.

65. For patients who do not have preexisting vertebral fracture or a baseline femoral neck T- score of -2.5SD or worse, the clinical trial evidence utterly fails to demonstrate a fracture reduction benefit. Thus, if there is any harm or risk of side effect from Fosamax, Fosamax is unreasonably dangerous because the risk of harm outweighs the benefit conferred.

66. For any group of patients who take Fosamax, the clinical trial evidence fails to demonstrate a fracture reduction benefit beyond three years of use. Thus, if there is any harm or risk of side effect from Fosamax, Fosamax is unreasonably dangerous after three years of use because the risk of harm outweighs the benefit conferred.

I declare under penalty of perjury pursuant to 18 USC § 1746 that the foregoing is true and correct. Executed on September 25, 2013.

/s/ Curt Daniel Furberg
CURT DANIEL FURBERG, M.D., Ph.D.

[Exhibit 7 to Ecklund Declaration]

Fosamax

David Madigan, PhD
October 15, 2012

1. Credentials

1. I am Professor and Chair of Statistics at Columbia University in New York City. I received my bachelor's degree in Mathematical Sciences from Trinity College Dublin in 1984 and was awarded the College's gold medal. In 1990, I received a Ph.D. in Statistics, also from Trinity College. I have worked in the past for KPMG, SkillSoft, University of Washington, AT&T Labs, and Soliloquy Inc. From 2005 to 2007 I was Professor of Statistics and Dean of Physical and Mathematical Sciences at Rutgers University. Prior to serving as Dean I was Director of the Rutgers University Institute of Biostatistics. I am an elected Fellow of both the Institute of Mathematical Statistics and the American Statistical Association and was the 36th most cited mathematician worldwide from 1995–2005. I was an Institute of Mathematical Statistics Medallion Lecturer in 2009. I recently completed a term as the Editor of *Statistical Science*, 2008–2010, the highest impact journal in Statistics.

2. I have published more than 100 technical papers on Bayesian statistics, biostatistics, pharmacovigilance, statistical graphics, Monte Carlo methods, computer-assisted learning, information retrieval, and text mining. Within the last few years I

have consulted for Boehringer-Ingelheim, Jarvik Heart, Novartis, Pfizer, Sanofi-Aventis, Takeda, and Wyeth on a variety of issues, many related to drug safety. I have considerable statistical experience with clinical trials including the design and analysis of pain studies at the University of Washington and the Fred Hutchinson Cancer Research Center, both in Seattle, and service as a statistical consultant to multiple internal and external clients, particularly while I was director of the Institute of Biostatistics at Rutgers University, and continuing with Jarvik Heart.

3. In the last several years, drug safety has been one of my significant research interests with a focus on the development and application of statistical methods for pharmacovigilance. I have published my work in *Drug Safety, Pharmacoepidemiology and Drug Safety, Epidemiology*, and other journals. I also serve as an investigator in the Mini-Sentinel project. Mini-Sentinel is a pilot project sponsored by the FDA to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. In 2010–11, I lead the Mini-Sentinel Working Group on case-based methods in active surveillance. In addition, I am the methods lead for the Observational Medical Outcomes Partnership, a public-private partnership between the FDA and the pharmaceutical industry. The partnership is conducting a multi-year initiative to research methods that are feasible and useful to analyze existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market. I am a member of the FDA's Drug Safety and Risk Management Advisory Committee (DSaRM). DSaRM

advises the FDA Commissioner on risk management, risk communication, and quantitative evaluation of spontaneous reports for drugs for human use and for any other product for which the FDA has regulatory responsibility. From 2010 to 2011 I was a member of a sub-committee of the FDA Science Board charged with reviewing the Center for Drug Evaluation and Research's pharmacovigilance program.

4. Further information concerning my background, training, and experience, including a complete list of my publications, is reflected in my curriculum vitae, a copy of which is attached as Appendix D. A list of the testimony I have provided in the last four years is attached as Appendix E.

2. Research Question

5. I was asked to examine whether a signal of problematic oversuppression of bone turnover and associated atypical femur fracture syndromes existed for Fosamax, using industry standard pharmacovigilance techniques and data sources, and the adverse event terms selected by Merck to internally evaluate the same. I was also asked to assess the strength of that signal, if any, in comparison to the signal, if any, for such events in other products indicated for the prevention and treatment of osteoporosis.

6. The approach I have taken to the work would have been the same had Merck hired me to carry out the analyses. I am being compensated at the rate of $500 per hour for my work on this matter. As I continue to review the data (or review newly provided data) I reserve the right to supplement and refine my

report. All the opinions I express herein I hold to a reasonable degree of scientific certainty.

3. Pharmacovigilance

7. Increasing scientific, regulatory and public scrutiny focuses on the obligation of the medical community, pharmaceutical industry, and health authorities to ensure that marketed drugs have acceptable benefit-risk profiles. This is an intricate and ongoing process that begins with pre-approval studies, but continues after regulatory market authorization when the drug is in widespread clinical use. In the latter environment, surveillance schemes based on spontaneous reporting system (SRS) databases represent a cornerstone for the early detection of drug hazards that are novel by virtue of their clinical nature, severity, and/or frequency. "Pharmacovigilance" is often used to describe the aforementioned surveillance activities.

8. Signal detection algorithms assist pharmacovigilance domain experts to discover potentially relevant drug-event associations. In recent years, data mining in pharmacovigilance has attracted significant attention and has now become routine both in the pharmaceutical industry and amongst regulators worldwide.

9. Pharmaceutical companies, health authorities, and drug monitoring centers use SRS databases for global screening for signals of new adverse events or changes in the frequency, character, or severity of existing adverse events (AEs) after regulatory authorization for use in clinical practice. The precise details of each SRS differ in terms of size and scope, statutory reporting mandates, surveillance selectivity

or intensity, and organizational count of 3[8]. For GPS, Szarfman and her co-authors proposed using a threshold of 2 for the EB05 measure[9] although other authors have suggested that EB05 is intrinsically too conservative in the sense that it could result in delayed detection of relevant signals. A recent review article[10] identified a wide variety of thresholds in actual use.

3.3 Signal Refinement

24. The methods I have just described represent standard approaches to signal detection in SRSs that are used by regulators and pharmaceutical companies worldwide. I note that such signal analyses are not meant to quantify the extent of a drug's increased risks. Once a signal is detected, a wide variety of approaches are used to carry out "signal refinement," a process designed to shed further light on the signal. One standard approach is to compare reporting rates of the drug in question with reporting rates for specific other drugs in the same class (using, for example, the PRR). This was the approach adopted when a signal

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[8] Evans, SJW, Waller, D, Davis, D. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiology and Drug Safety*, **10**,(2001) 483–486.

[9] Szarfman A, Machado SG, O'Neill RT: Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf* (2002) **25**(6):381–392.

[10] Deshpande, G., Gogolak, V., Weiss Smith, S. Data Mining in Drug Safety: Review of Published Threshold Criteria for Defining Signals of Disproportionate Reporting. *Pharmaceutical Medicine*. **24**(1):37–43, February 1, 2010.

was generated for Baycol (cerivastatin) and rhabdomyolysis. In that context, the scientific community focused on the reporting rate for rhabdomyolysis and Baycol as compared with other market-leading statins[11].

4. Methods

25. Using the FDA's AERS database, I examined the possible association between Fosamax and a series of MEDRA preferred terms selected by Merck to evaluate oversuppression of bone turnover and associated atypical femur fracture syndromes. I used two industry-standard signal detection algorithms (MGPS and PRR as described in Section 3) to assess whether or not Fosamax presented a safety signal related to oversuppression of bone turnover. Specifically I considered the EB05, EBGM, and PRR metrics over time. As a comparator, I considered the other approved oral bisphosphonates indicated for the treatment and prevention of osteoporosis (risedronate and ibandronate), as well a non-bisphosphonate drug indicated for the treatment and prevention of osteoporosis (raloxifene)[12]. Risedronate was first approved in March 1998, ibandronate was first approved in May 2003, and raloxifene was first

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[11] Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. *Curr Control Trials Cardiovasc Med*, 2(5) 205–207.

[12] FDA Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee, September 9th, 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm270958.pdf

approved in December 1997. Since ibandronate is available in both oral and injectable form, I excluded reports where the route of administration was injection. Some analysts have observed declining reporting rates over time. Since alendronate was approved before the comparator drugs, this should result in conservative estimates of the relative risk associated with alendronate.

26. As endpoints, I considered the MedDRA preferred terms that Merck selected in their examination of oversuppression of bone turnover and associated atypical femur fracture syndromes[13]. These terms are:

- bone development abnormal
- bone disorder
- bone formation decreased
- fracture delayed union
- fracture malunion
- fracture nonunion
- low turnover osteopathy
- pathological fracture
- stress fracture
- fracture
- femur fracture

I note an internal Merck email discusses combining three preferred terms that have delayed union as a feature so I also consider the composite endpoint of fracture delayed union, fracture malunion, and

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[13] MRK-FOSMDL-BOL-00008312 at 13, MRK-FOSMDL-BOL-00015857 at 60, MRK-FOSMDL-01020264 at 435,

fracture nonunion[14] and refer to this endpoint as "fracture union issues."

27. To conduct my analyses I used the programming language perl (for data preparation), the statistical software package R (version 2.15.0), and the QScan pharmacovigilance platform provided by DrugLogic Inc. (Reston, VA). Specicially I used QScan to compute EBGM, EB05, and PRR statistics and to generate summary statistics required for my analysis.

28. The QScan software has been in widespread use for over 10 years and has been validated extensively. DrugLogic uses a very detailed validation process (originally set up by an FDA software auditor.) DrugLogic's software development process is CFR 21 Part 11 compliant. Many peer-reviewed publications report results derived from QScan[15].

29. Publications reporting disproportionality analyses often report stratified results. All results presented below are stratified by sex (male, female, unknown) and age (unknown, 0–15, 16–30, 31–50, 51–75, and greater than 75). As a sensitivity analysis, I performed several calculations without stratification

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[14] MRK-FOSMDL-GOL-00017912 at 14

[15] See, for example, Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. *Pharmacoepidemiology and Drug Safety*, 14,(2005) 747–753 or Alsheikh-Ali AA, Karas RH, Adverse Events With Concomitant Amiodarone and Statin Therapy, *Preventative Cardiology*, 8, (2005), 95–97 or Ratcliffe S, Younus M, Hauben M, Reich L. Antidepressants that inhibit neuronal norepinephrine reuptake are not associated with increased spontaneous reporting of cardiomyopathy. *Journal of Psychopharmacology*, 24, (2010), 503–511.

and unstratified PRR and EB05 values never differed by more than 0.5 from their stratified counterparts.

30. Duplicate reports can occur in SRS systems and a number of authors have described algorithms for detecting duplicates. In the analyses presented below I removed duplicates defined as reports having identical manufacturer and control codes.

31. Historically MGPS calculations have often omitted drugs with fewer than 100 reports overall and AEs with fewer than 100 reports. This is largely to reduce the computational burden and has little effect on the analyses. In what follows I do not impose such a limitation.

32. In some of my publications[16] I have expressed concern about confounding bias introduced by the so-called "innocent bystander" effect. The basic problem is as follows. Suppose Drug A causes a particular adverse event and Drug B does not. Further suppose that Drug A is commonly co-prescribed with Drug B. Then any analysis of Drug B will tend to incorrectly show an association with the adverse event. Drug B is an "innocent bystander." Statistical methods do exist to account for this problem[17] although these have yet to find widespread adoption.

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[16] Hauben, M., Madigan, D., Gerrits, C., and Meyboom, R. (2005). The role of data mining in pharmacovigilance. *Expert Opinion in Drug Safety*, **4**(5), 929–948.

[17] Caster, O., Noren, G.N., Madigan, D., and Bate, A. (2010). Large-Scale Regression-Based Pattern Discovery: The Example of Screening the WHO Global Drug Safety Database. *Statistical Analysis and Data Mining*, **3**, 197–208.

33. In the specific case of Fosamax, many different drugs are co-reported. However, the co-reported medications are very similar between Fosamax and the comparator drugs. Thus, if a signal of disproportionate reporting is due to an innocent bystander, the same signal should be present for all the drugs I consider. Since the results below demonstrate differential signals for Fosamax, the innocent bystander effect cannot explain the findings and is not a concern in my analysis.

5. Results

34. Appendix A presents cumulative results as of December 31st each year from 2001 to 2011. I also present results through the end of the first quarter of 2012, which includes the most recent AERS data available. For each endpoint (11 preferred terms and the composite fracture union endpoint) and for each comparator drug, the Tables below provide:

- EB05 (Appendix A1),
- EBGM (Appendix A2),
- PRR (Appendix A3), and
- the observed number of reports (Appendix A4)

for each timepoint.

6. Discussion

35. My analyses clearly demonstrate the existence of early signals for Fosamax for various terms related to oversuppression of bone turnover and associated atypical femur fracture concerns. Focusing on the conservative EB05 measure, and applying a signaling threshold of 2, Table 1 below shows the year when a signal first emerged.

	Alendronate	Risedronate & Ibandronate	Raloxifene
fracture delayed union	2004	2011	No signal
fracture malunion	2002	2010	No signal
fracture nonunion	2005	2010	No signal
fracture union issues	2002	2009	No signal
bone development abnormal	No signal	No signal	No signal
bone disorder	2001	2007	No signal
bone formation decreased	2004	No signal	No signal
low turnover osteopathy	2005	2010	No signal
fracture	2005	2004	2004
femur fracture	2005	2009	2006
pathological fracture	2009	2010	No signal
stress fracture	2003	2009	2004

For only one of the eleven events selected by Merck as relevant to assessing bone oversuppression and fracture risks was a signal not evident (bone development abnormal). For each of the others, a safety signal was evident. The composite endpoint

fracture union issues revealed a very strong early signal (EB05 = 2.39 in 2002), which only got stronger over time (e.g., EB05 = 20.63 in 2012). With a single exception ("fracture"), alendronate signaled earlier than the comparators for every event considered. For eight of the twelve outcomes considered, Fosamax signaled five or more years before the comparators.

7. Conclusion

36. Based on my review of FDA spontaneous report data for Fosamax, it is apparent that industry standard pharmacovigilance techniques and datasources reveal the presence of a clear signal for oversuppression of bone turnover and associated atypical femur fracture events utilizing the terms selected by Merck for such analysis. By standard metrics of "signal" detection, the signal is strong, consistent, and not ambiguous. Of perhaps greater concern, the signal was striking in comparison to that for other drugs indicated for the prevention and treatment of osteoporosis. As early as 2001–2002, the spontaneous report data for Fosamax provide signals for a number of indicators of suppression of bone turnover. For the comparator drugs, such signals either never appear or appear years later.

s/ David Madigan
David Madigan, PhD
October 15, 2012

[Exhibit 9 to Ecklund Declaration]

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA
[illegible]

FOSAMAX®

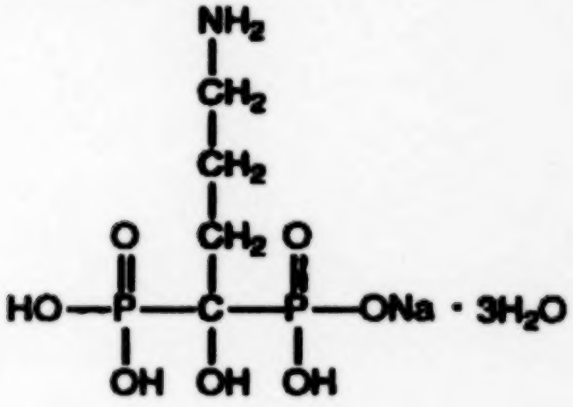
(ALENDRONATE SODIUM) TABLETS AND ORAL SOLUTION

DESCRIPTION

FOSAMAX® (alendronate sodium) is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

The empirical formula of alendronate sodium is $C_4H_{12}NNaO_7P_23H_2O$ and its formula weight is 325.12. The structural formula is:



Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Tablets FOSAMAX for oral administration contain 6.53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. Tablets FOSAMAX 10 mg also contain carnauba wax.

Each bottle of the oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid. Each bottle also contains the following inactive ingredients: sodium citrate dihydrate and citric acid anhydrous as buffering agents, sodium saccharin, artificial raspberry flavor, and purified water. Added as preservatives are sodium propylparaben 0.0225% and sodium butylparaben 0.0075%.

CLINICAL PHARMACOLOGY

Mechanism of Action

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [^{3}H]alendronate in bone showed about

10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While incorporated in bone matrix, alendronate is not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

Pharmacokinetics

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg tablet in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

FOSAMAX 70 mg oral solution and FOSAMAX 70 mg tablet are equally bioavailable.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to

dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Distribution

Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

Metabolism

There is no evidence that alendronate is metabolized in animals or humans.

Excretion

Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min (64, 78; 90% confidence interval [CI]), and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than

95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with FOSAMAX (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations

Pediatric: The oral bioavailability in children was similar to that observed in adults; however, FOSAMAX is not indicated for use in children (see PRECAUTIONS, *Pediatric Use*).

Gender: Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Geriatric: Bioavailability and disposition (urinary excretion) were similar in elderly and younger patients. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore,

somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). **FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience with alendronate in renal failure.**

Hepatic Insufficiency: As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.

Drug Interactions

(also see PRECAUTIONS, *Drug Interactions*)

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.

Pharmacodynamics

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate

reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Osteoporosis in postmenopausal women

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral (spinal) fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to age 90, the risk of hip fracture in white women increases 50-fold and the risk of vertebral fracture 15- to 30-fold. It is estimated that approximately 40% of 50-year-old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These

biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with FOSAMAX 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received FOSAMAX 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with FOSAMAX. In osteoporosis treatment studies FOSAMAX 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25 to 30% to reach a plateau after 6 to 12 months. In osteoporosis prevention studies FOSAMAX 5 mg/day decreased osteocalcin and total serum alkaline phosphatase by approximately 40% and 15%, respectively. Similar reductions in the rate of bone turnover were observed in postmenopausal women during one-year studies with once weekly FOSAMAX 70 mg for the treatment of osteoporosis and once weekly FOSAMAX 35 mg for the prevention of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with FOSAMAX. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of FOSAMAX 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment; however, serum phosphate returned toward prestudy levels during years three through five. Similar reductions were observed with FOSAMAX 5 mg/day. In one-year studies with once weekly FOSAMAX 35 and 70 mg, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to FOSAMAX but also a decrease in renal phosphate reabsorption.

Osteoporosis in men

Treatment of men with osteoporosis with FOSAMAX 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a one-year study in men with osteoporosis receiving once weekly FOSAMAX 70 mg.

Glucocorticoid-induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs both in males and females of all ages. Osteoporosis occurs as a result of inhibited bone

formation and increased bone resorption resulting in net bone loss. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of up to two years' duration, FOSAMAX 5 and 10 mg/day reduced cross-linked N-telopeptides of type I collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 15 to 30% and 8 to 18%, respectively. As a result of inhibition of bone resorption, FOSAMAX 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1 to 2%) and serum phosphate (approximately 1 to 8%).

Paget's disease of bone

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

FOSAMAX decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, FOSAMAX 40 mg once daily for six months produced significant decreases in

serum alkaline phosphatase as well as in urinary markers of bone collagen degradation. As a result of the inhibition of bone resorption, FOSAMAX induced generally mild, transient, and asymptomatic decreases in serum calcium and phosphate.

Clinical Studies

Treatment of osteoporosis

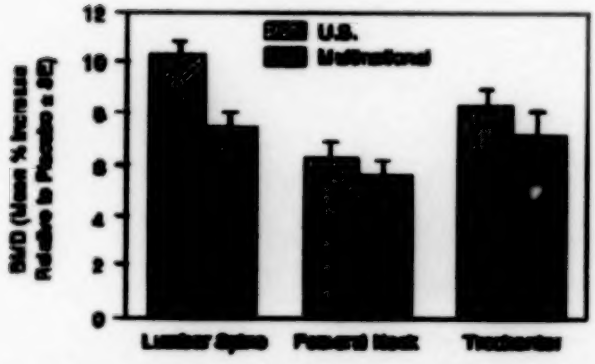
Postmenopausal women

Effect on bone mineral density

The efficacy of FOSAMAX 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration. These included two three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 10 mg/day relative to placebo-treated patients at three years for each of these studies.

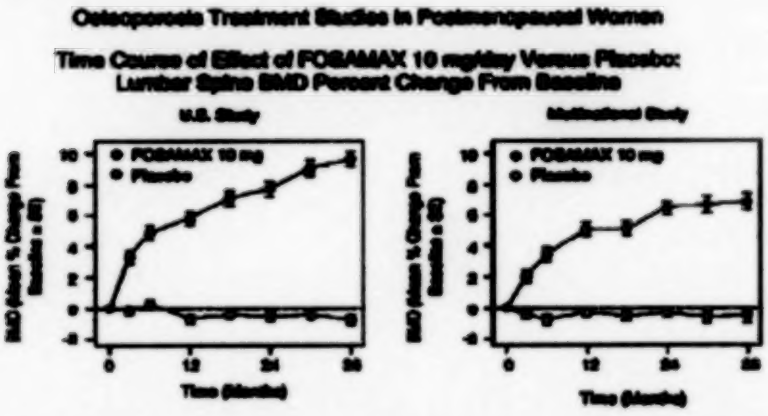
Osteoporosis Treatment Studies in Postmenopausal Women

Increase in BMD
FOSAMAX 10 mg/day at Three Years



At three years significant increases in BMD, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received FOSAMAX 10 mg/day. Total body BMD also increased significantly in each study, suggesting that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the three years of treatment. (See figures below for lumbar spine results.) In the two-year extension of these studies, treatment of 147 patients with FOSAMAX 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total body were maintained. FOSAMAX was similarly effective regardless of age, race, baseline rate of bone turnover, and baseline BMD in the range studied (at

least 2 standard deviations below the premenopausal mean).



In patients with postmenopausal osteoporosis treated with FOSAMAX 10 mg/day for one or two years, the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those of the placebo groups.

The therapeutic equivalence of once weekly FOSAMAX 70 mg (n=519) and FOSAMAX 10 mg daily (n=370) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the 70-mg once-weekly group (n=440) and 5.4% (5.0, 5.8%; 95% CI) in the 10-mg daily group (n=330). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Effect on fracture incidence

Data on the effects of FOSAMAX on fracture incidence are derived from three clinical studies: 1) U.S. and Multinational combined: a study of patients with a BMD T-score at or below minus 2.5 with or without a prior vertebral fracture, 2) Three-Year Study of the Fracture Intervention Trial (FIT): a study of patients with at least one baseline vertebral fracture, and 3) Four-Year Study of FIT: a study of patients with low bone mass but without a baseline vertebral fracture.

To assess the effects of FOSAMAX on the incidence of vertebral fractures (detected by digitized radiography; approximately one third of these were clinically symptomatic), the U.S. and Multinational studies were combined in an analysis that compared placebo to the pooled dosage groups of FOSAMAX (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a statistically significant reduction in the proportion of patients treated with FOSAMAX experiencing one or more new vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%; a 48% relative risk reduction). A reduction in the total number of new vertebral fractures (4.2 vs. 11.3 per 100 patients) was also observed. In the pooled analysis, patients who received FOSAMAX had a loss in stature that was statistically significantly less than was observed in those who received placebo (-3.0 mm vs. -4.6 mm).

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline radiographic vertebral fracture and the Four-Year

Study of patients with low bone mass but without a baseline vertebral fracture. In both studies of FIT, 96% of randomized patients completed the studies (i.e., had a closeout visit at the scheduled end of the study); approximately 80% of patients were still taking study medication upon completion.

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 2027-patient study (FOSAMAX, n=1022; placebo, n=1005) demonstrated that treatment with FOSAMAX resulted in statistically significant reductions in fracture incidence at three years as shown in the table below.

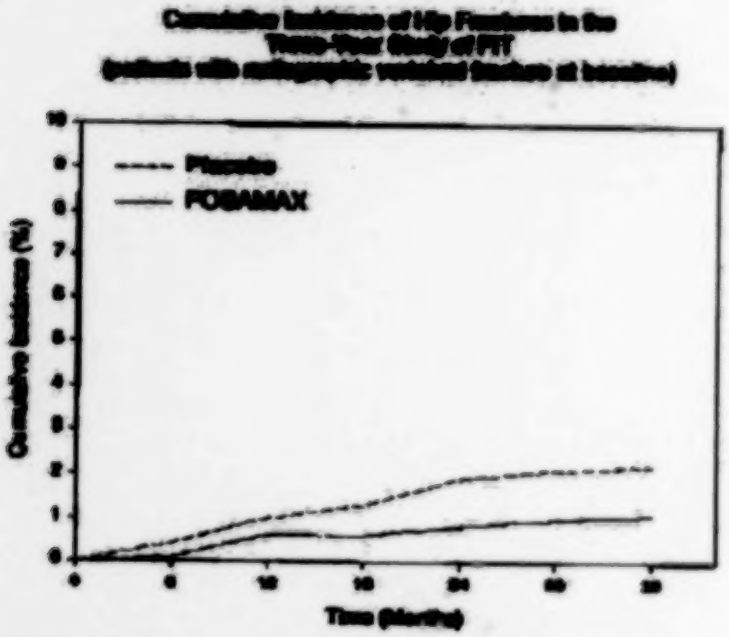
[illegible]

	Percent of Patients			
	FOSAMAX (n=1022)	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk [illegible]
Patients with:				
Vertebral fractures (diagnosed by X-ray)[a]				
≥ 1 new vertebral fracture	7.9	15.0	7.1	47[illegible]
≥ 2 new vertebral fractures	0.5	4.9	4.4	[illegible]
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	13.8	18.1	4.3	24[illegible]
≥ 1 clinical (symptomatic) vertebral fracture	2.3	5.0	2.7	54[illegible]
Hip fracture	1.1	2.2	1.1	[illegible]
Wrist (forearm) fracture	2.2	4.1	1.9	[illegible]

[illegible]

Furthermore, in this population of patients with baseline vertebral fracture, treatment with FOSAMAX significantly reduced the incidence of hospitalizations (25.0% vs. 30.7%).

In the Three-Year Study of FIT, fractures of the hip occurred in 22 (2.2%) of 1005 patients on placebo and 11 (1.1%) of 1022 patients on FOSAMAX, p=0.047. The figure below displays the cumulative incidence of hip fractures in this study.



Fracture Intervention Trial: Four-Year Study (patients with low bone mass but without a baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 4432-patient study (FOSAMAX, n=2214; placebo, n=2218) further investigated the reduction in fracture incidence due to FOSAMAX. The intent of the study was to recruit women with osteoporosis, defined as a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the

normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the table below for the patients with osteoporosis.

[illegible]

Fracture results across studies

In the Three-Year Study of FIT, FOSAMAX reduced the percentage of women experiencing at least one new radiographic vertebral fracture from 15.0% to 7.9% (47% relative risk reduction, $p<0.001$); in the Four-Year Study of FIT, the percentage was reduced from 3.8% to 2.1% (44% relative risk reduction, $p=0.001$); and in the combined U.S./Multinational studies, from 6.2% to 3.2% (48% relative risk reduction, $p=0.034$).

FOSAMAX reduced the percentage of women experiencing multiple (two or more) new vertebral fractures from 4.2% to 0.6% (87% relative risk reduction, $p<0.001$) in the combined U.S./Multinational studies and from 4.9% to 0.5%

(90% relative risk reduction, $p<0.001$) in the Three-Year Study of FIT. In the Four-Year Study of FIT, FOSAMAX reduced the percentage of osteoporotic women experiencing multiple vertebral fractures from 0.6% to 0.1% (78% relative risk reduction, $p=0.035$).

Thus, FOSAMAX reduced the incidence of radiographic vertebral fractures in osteoporotic women whether or not they had a previous radiographic vertebral fracture.

FOSAMAX, over a three- or four-year period, was associated with statistically significant reductions in loss of height vs. placebo in patients with and without baseline radiographic vertebral fractures. At the end of the FIT studies the between-treatment group differences were 3.2 mm in the Three-Year Study and 1.3 mm in the Four-Year Study.

Bone histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with FOSAMAX at doses ranging from 1 to 20 mg/day for one, two, or three years revealed normal mineralization and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in rats and baboons exposed to long-term alendronate treatment, support the conclusion that bone formed during therapy with FOSAMAX is of normal quality.

Men

The efficacy of FOSAMAX in men with hypogonadal or idiopathic osteoporosis was demonstrated in two clinical studies.

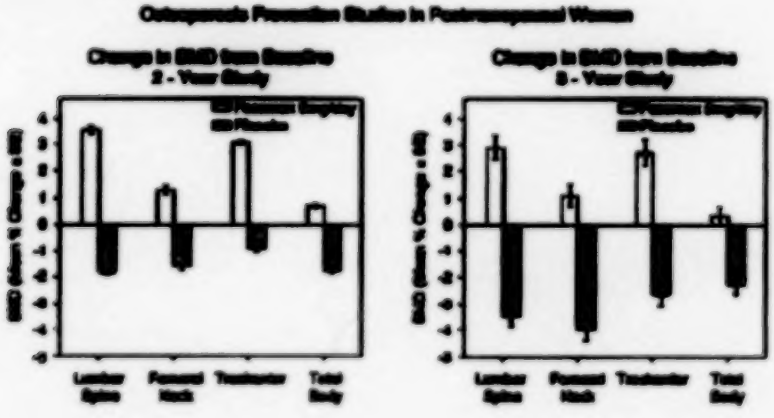
A two-year, double-blind, placebo-controlled, multicenter study of FOSAMAX 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). All patients in the trial had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, or 2) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At two years, the mean increases relative to placebo in BMD in men receiving FOSAMAX 10 mg/day were significant at the following sites: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Treatment with FOSAMAX also reduced height loss (FOSAMAX, -0.6 mm vs. placebo, -2.4 mm).

A one-year, double-blind, placebo-controlled, multicenter study of once weekly FOSAMAX 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, 2) a BMD T-score ≤-2 at the lumbar spine and ≤-1 at the femoral neck, or 3) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At one year, the mean increases relative to placebo in BMD in men receiving FOSAMAX 70 mg once weekly were significant at the following sites: lumbar spine, 2.8%; femoral neck, 1.9%; trochanter, 2.0%; and total body, 1.2%. These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.

In both studies, BMD responses were similar regardless of age (≥65 years vs. <65 years), gonadal function (baseline testosterone <9 ng/dL vs. ≥9 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score ≤-2.5 vs. >-2.5).

Prevention of osteoporosis in postmenopausal women

Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal women 40–60 years of age. One thousand six hundred nine patients (FOSAMAX 5 mg/day; n=498) who were at least six months postmenopausal were entered into a two-year study without regard to their baseline BMD. In the other study, 447 patients (FOSAMAX 5 mg/day; n=88), who were between six months and three years postmenopause, were treated for up to three years. In the placebo-treated patients BMD losses of approximately 1% per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, FOSAMAX 5 mg/day prevented bone loss in the majority of patients and induced significant increases in mean bone mass at each of these sites (see figures below). In addition, FOSAMAX 5 mg/day reduced the rate of bone loss at the forearm by approximately half relative to placebo. FOSAMAX 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.



The therapeutic equivalence of once weekly FOSAMAX 35 mg (n=362) and FOSAMAX 5 mg daily (n=361) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women without osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 2.9% (2.6, 3.2%; 95% CI) in the 35-mg once-weekly group (n=307) and 3.2% (2.9, 3.5%; 95% CI) in the 5-mg daily group (n=298). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Bone histology

Bone histology was normal in the 28 patients biopsied at the end of three years who received FOSAMAX at doses of up to 10 mg/day.

Concomitant use with estrogen/hormone replacement therapy (HRT)

The effects on BMD of treatment with FOSAMAX 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo- controlled study of hysterectomized postmenopausal osteoporotic women (n=425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either estrogen or FOSAMAX alone (both 6.0%).

The effects on BMD when FOSAMAX was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n=428). The addition of

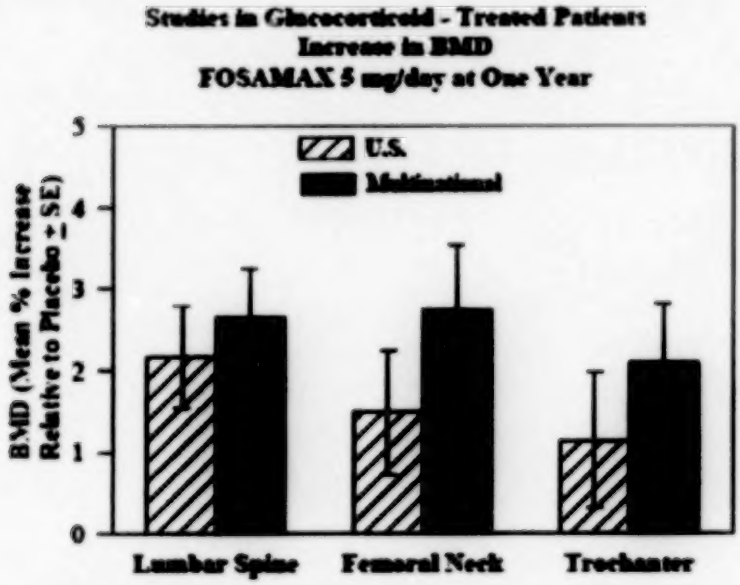
FOSAMAX 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favorable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD.

Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with FOSAMAX and HRT, 94% on FOSAMAX alone, and 78% on HRT alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence and fracture healing have not been studied.

Glucocorticoid-induced osteoporosis

The efficacy of FOSAMAX 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year, double-blind, randomized, placebo-controlled, multicenter studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational [which also included FOSAMAX 2.5 mg/day]). These studies enrolled 232 and 328 patients, respectively, between the ages of 17 and 83 with a variety of glucocorticoid-requiring diseases. Patients received supplemental calcium and vitamin D. The following figure shows the mean increases relative to placebo in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 5 mg/day for each study.



After one year, significant increases relative to placebo in BMD were seen in the combined studies at each of these sites in patients who received FOSAMAX 5 mg/day. In the placebo-treated patients, a significant decrease in BMD occurred at the femoral neck (-1.2%), and smaller decreases were seen at the lumbar spine and trochanter. Total body BMD was maintained with FOSAMAX 5 mg/day. The increases in BMD with FOSAMAX 10 mg/day were similar to those with FOSAMAX 5 mg/day in all patients except for postmenopausal women not receiving estrogen therapy. In these women, the increases (relative to placebo) with FOSAMAX 10 mg/day were greater than those with FOSAMAX 5 mg/day at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. FOSAMAX was effective regardless of dose or duration of glucocorticoid use. In addition, FOSAMAX was similarly effective regardless of age

(<65 vs. ≥65 years), race (Caucasian vs. other races), gender, underlying disease, baseline BMD, baseline bone turnover, and use with a variety of common medications.

Bone histology was normal in the 49 patients biopsied at the end of one year who received FOSAMAX at doses of up to 10 mg/day.

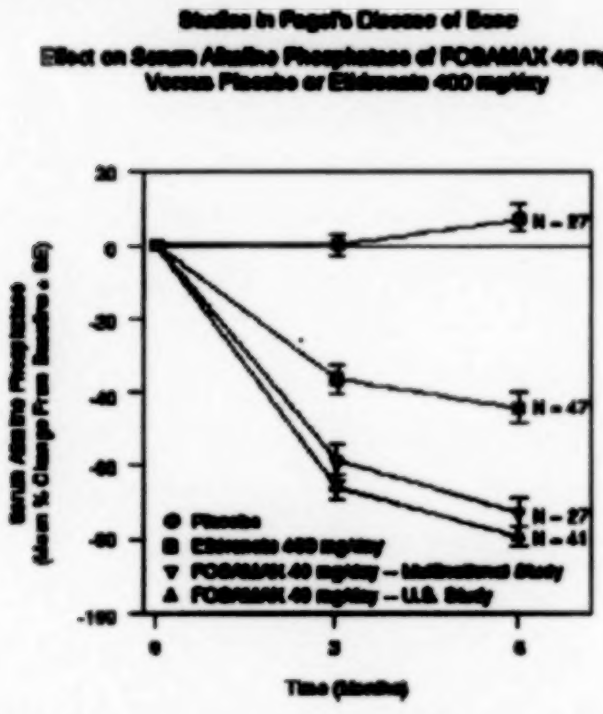
Of the original 560 patients in these studies, 208 patients who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year double-blind extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with FOSAMAX 5 and 10 mg/day, respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.

After one year, 2.3% of patients treated with FOSAMAX 5 or 10 mg/day (pooled) vs. 3.7% of those treated with placebo experienced a new vertebral fracture (not significant). However, in the population studied for two years, treatment with FOSAMAX (pooled dosage groups: 5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) significantly reduced the incidence of patients with a new vertebral fracture (FOSAMAX 0.7% vs. placebo 6.8%).

Paget's disease of bone

The efficacy of FOSAMAX 40 mg once daily for six months was demonstrated in two double-blind clinical studies of male and female patients with moderate to severe Paget's disease (alkaline phosphatase at least twice the upper limit of normal): a placebo-controlled, multinational study and a U.S. comparative study

with etidronate disodium 400 mg/day. The following figure shows the mean percent changes from baseline in serum alkaline phosphatase for up to six months of randomized treatment.



At six months the suppression in alkaline phosphatase in patients treated with FOSAMAX was significantly greater than that achieved with etidronate and contrasted with the complete lack of response in placebo-treated patients. Response (defined as either normalization of serum alkaline phosphatase or decrease from baseline >60%) occurred in approximately 85% of patients treated with FOSAMAX in the combined studies vs. 30% in the etidronate group and 0% in the placebo group. FOSAMAX was similarly effective regardless of age,

gender, race, prior use of other bisphosphonates, or baseline alkaline phosphatase within the range studied (at least twice the upper limit of normal).

Bone histology was evaluated in 33 patients with Paget's disease treated with FOSAMAX 40 mg/day for 6 months. As in patients treated for osteoporosis (see *Clinical Studies, Treatment of osteoporosis in postmenopausal women, Bone histology*), FOSAMAX did not impair mineralization, and the expected decrease in the rate of bone turnover was observed. Normal lamellar bone was produced during treatment with FOSAMAX, even where preexisting bone was woven and disorganized. Overall, bone histology data support the conclusion that bone formed during treatment with FOSAMAX is of normal quality.

ANIMAL PHARMACOLOGY

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

INDICATIONS AND USAGE

FOSAMAX is indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women
  - For the treatment of osteoporosis, FOSAMAX increases bone mass and reduces

the incidence of fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics*.)

- For the prevention of osteoporosis, FOSAMAX may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture.

  Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of FOSAMAX for prevention of osteoporosis.

- Treatment to increase bone mass in men with osteoporosis
- Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to

7.5 mg or greater of prednisone and who have low bone mineral density (see PRECAUTIONS, *Glucocorticoid-induced osteoporosis*). Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.

- Treatment of Paget's disease of bone in men and women
  - Treatment is indicated in patients with Paget's disease of bone having alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

The safety and effectiveness of FOSAMAX for the treatment of osteoporosis are based on clinical data of four years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes (see WARNINGS)
- Patients at increased risk of aspiration should not receive FOSAMAX oral solution.
- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, *General*)

WARNINGS

FOSAMAX, like other bisphosphonates administered orally, may cause local irritation of the

upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis, or ulcers).

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates including FOSAMAX. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates including FOSAMAX and/or who fail to swallow oral bisphosphonates including FOSAMAX with the recommended full glass (6–8 oz) of water, and/or who continue to take oral bisphosphonates including FOSAMAX after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to mental disability,

therapy with FOSAMAX should be used under appropriate supervision.

There have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

General

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FOSAMAX.

Presumably due to the effects of FOSAMAX on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Musculoskeletal Pain

In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). This category of drugs includes FOSAMAX (alendronate). Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups.

Dental

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including FOSAMAX. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (e.g., tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures).

For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk for ONJ. Clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit/risk assessment.

Patients who develop osteonecrosis of the jaw while on bisphosphonate therapy should receive care by an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Renal insufficiency

FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Glucocorticoid-induced osteoporosis

The risk versus benefit of FOSAMAX for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see INDICATIONS AND USAGE). Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined FOSAMAX and glucocorticoid treatment.

The efficacy of FOSAMAX for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of FOSAMAX has been established in studies of two years' duration. The greatest increase

in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of FOSAMAX beyond two years has not been studied.

The efficacy of FOSAMAX in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in postmenopausal women. The efficacy for prevention of non-vertebral fractures has not been demonstrated.

Information for Patients

General

Physicians should instruct their patients to read the Medication Guide before starting therapy with FOSAMAX and to reread it each time the prescription is renewed.

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Dosing Instructions

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when it is taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Absorption*).

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of FOSAMAX with a full glass of water (6–8 oz). To facilitate gastric emptying patients should drink at least 2 oz (a quarter of a cup) of water after taking FOSAMAX oral solution. Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking FOSAMAX and consult their physician.

Patients should be instructed that if they miss a dose of once weekly FOSAMAX, they should take one dose on the morning after they remember. They should not take two doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.

Drug Interactions
(also see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Drug Interactions)*

Estrogen/hormone replacement therapy (HRT)

Concomitant use of HRT (estrogen ± progestin) and FOSAMAX was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic

women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence have not been studied (see CLINICAL PHARMACOLOGY, *Clinical Studies, Concomitant use with estrogen/hormone replacement therapy (HRT)* and ADVERSE REACTIONS, *Clinical Studies, Concomitant use with estrogen/hormone replacement therapy*).

Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of FOSAMAX. Therefore, patients must wait at least one-half hour after taking FOSAMAX before taking any other oral medications.

Aspirin

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of FOSAMAX greater than 10 mg and aspirin-containing products.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

FOSAMAX may be administered to patients taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking FOSAMAX 5 or 10 mg/day compared to those taking placebo. However, since NSAID use is

associated with gastrointestinal irritation, caution should be used during concomitant use with FOSAMAX.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m2. The relevance of this finding to humans is unknown.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Pregnancy

Pregnancy Category C:

Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal

deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

There are no studies in pregnant women. FOSAMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSAMAX is administered to nursing women.

Pediatric Use

The efficacy and safety of FOSAMAX were examined in a randomized, double-blind, placebo-controlled two-year study of 139 pediatric patients, aged 4-18 years, with severe osteogenesis imperfecta. One-hundred-and-nine patients were randomized to 5

mg FOSAMAX daily (weight <40 kg) or 10 mg FOSAMAX daily (weight ≥40 kg) and 30 patients to placebo. The mean baseline lumbar spine BMD Z-score of the patients was -4.5. The mean change in lumbar spine BMD Z-score from baseline to Month 24 was 1.3 in the FOSAMAX-treated patients and 0.1 in the placebo-treated patients. Treatment with FOSAMAX did not reduce the risk of fracture. Sixteen percent of the FOSAMAX patients who sustained a radiologically-confirmed fracture by Month 12 of the study had delayed fracture healing (callus remodeling) or fracture non-union when assessed radiographically at Month 24 compared with 9% of the placebo-treated patients. In FOSAMAX-treated patients, bone histomorphometry data obtained at Month 24 demonstrated decreased bone turnover and delayed mineralization time; however, there were no mineralization defects. There were no statistically significant differences between the FOSAMAX and placebo groups in reduction of bone pain.

FOSAMAX is not indicated for use in children.

(For clinical adverse experiences in children, see ADVERSE REACTIONS, *Clinical Studies, Osteogenesis Imperfecta.*)

Geriatric Use

Of the patients receiving FOSAMAX in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years of age and 17% (n=550) were ≥75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see CLINICAL PHARMACOLOGY, *Clinical*

Studies), 45%, 54%, 37%, and 70%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Clinical Studies

In clinical studies of up to five years in duration adverse experiences associated with FOSAMAX usually were mild, and generally did not require discontinuation of therapy.

FOSAMAX has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of osteoporosis

Postmenopausal women

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: FOSAMAX, 3.2%; placebo, 2.7%. In these study populations, 49–54% had a history of gastrointestinal disorders at baseline and

54–89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX or placebo are presented in the following table.

[illegible]

	[illegible]		Fracture Intervention Trial	
	FOSAMAX® 0 (n=196)	Placebo 0 (n=397)	FOSAMAX® 0 (n=3736)	Placebo 0 (n=3723)
[illegible]				
abdominal pain	6.6	4.8	1.5	1.5
nausea	3.6	4.8	1.1	1.5
dyspepsia	3.6	3.5	1.1	1.2
constipation	3.1	1.8	0.8	0.2
diarrhea	3.1	1.8	0.6	0.3
flatulence	2.6	0.5	0.2	0.3
acid regurgitation	2.0	4.3	1.1	0.9
esophageal ulcer	1.5	0.0	0.1	0.1
vomiting	1.0	1.5	0.2	0.3
dysphagia	1.0	0.0	0.1	0.1
abdominal distention	1.0	0.8	0.0	0.0
gastritis	0.5	1.3	0.6	0.7
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	4.1	2.5	0.4	0.3
muscle cramp	0.0	1.0	0.2	0.1
Nervous System/Psychiatric				
headache	2.6	1.5	0.2	0.2
dizziness	0.0	1.0	0.0	0.1
Special Senses				
taste perversion	0.5	1.0	0.1	0.0

[illegible]
[illegible]

Rarely, rash and erythema have occurred.

One patient treated with FOSAMAX (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of

FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of FOSAMAX in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with FOSAMAX 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 70 mg and FOSAMAX 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group are presented in the following table.

[redacted]

Men

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 10 mg/day and a one-year study of once weekly

FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for FOSAMAX 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly FOSAMAX 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥2% of patients treated with either FOSAMAX or placebo are presented in the following table.

[illegible]

	[illegible]			
	[illegible]		[illegible]	
	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]				
[illegible]	4.1	3.2	0.0	0.0
[illegible]	4.1	1.1	0.0	0.0
[illegible]	0.7	3.2	2.8	0.0
[illegible]				
[illegible]	3.4	0.0	2.8	1.7
[illegible]	1.4	1.1	2.8	0.0
[illegible]	2.1	1.1	0.0	3.4
[illegible]	2.1	0.0	0.0	0.0

Prevention of osteoporosis in postmenopausal women

The safety of FOSAMAX 5 mg/day in postmenopausal women 40–60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive FOSAMAX for either two or three years. In these studies the overall safety profiles of FOSAMAX 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with FOSAMAX 5 mg/day and 5.7% of 648 patients treated with placebo.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 35 mg and FOSAMAX 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either once weekly FOSAMAX 35 mg, FOSAMAX 5 mg/day or placebo are presented in the following table.

[illegible]

Concomitant use with estrogen/hormone replacement therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with FOSAMAX 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Treatment of glucocorticoid-induced osteoporosis

In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in >1% of patients treated with either FOSAMAX 5 or 10 mg/day or placebo are presented in the following table.

[redacted]

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year.

Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3–12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One

case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo.

Osteogenesis Imperfecta

FOSAMAX is not indicated for use in children.

The overall safety profile of FOSAMAX in OI patients treated for up to 24 months was generally similar to that of adults with osteoporosis treated with FOSAMAX. However, there was an increased occurrence of vomiting in OI patients treated with FOSAMAX compared to placebo. During the 24-month treatment period, vomiting was observed in 32 of 109 (29.4%) patients treated with FOSAMAX and 3 of 30 (10%) patients treated with placebo.

In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of FOSAMAX 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration. These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with an acute-phase response that has been reported in patients receiving bisphosphonates,

including FOSAMAX. See ADVERSE REACTIONS, *Post-Marketing Experience, Body as a Whole.*

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with FOSAMAX, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, *Information for Patients*, and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection

with delayed healing, has been reported rarely (see PRECAUTIONS, *Dental*).

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, Musculoskeletal Pain); joint swelling; low-energy femoral shaft and subtrochanteric fractures (see PRECAUTIONS, Atypical Subtrochanteric and Diaphyseal Femoral Fractures).

Nervous system: dizziness and vertigo.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m^2).

No specific information is available on the treatment of overdosage with FOSAMAX. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

FOSAMAX must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only (see PRECAUTIONS, *Information for Patients*). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of FOSAMAX (see PRECAUTIONS, *Drug Interactions*). Waiting less than 30 minutes, or taking FOSAMAX with food, beverages (other than plain water) or other medications will lessen the effect of FOSAMAX by decreasing its absorption into the body.

FOSAMAX should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, a FOSAMAX tablet should be swallowed with a full glass of water (6–8 oz). To facilitate gastric emptying FOSAMAX oral solution should be followed by at least 2 oz (a quarter of a cup) of water. Patients should not lie down for at least 30 minutes and until after their first food of the day. FOSAMAX should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see WARNINGS, PRECAUTIONS, *Information for Patients*).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see PRECAUTIONS, *General*).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX is not recommended for patients with more severe renal

insufficiency (creatinine clearance <35 mL/min) due to lack of experience.

Treatment of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 70 mg tablet once weekly

  or

- one bottle of 70 mg oral solution once weekly

  or

- one 10 mg tablet once daily

Treatment to increase bone mass in men with osteoporosis

The recommended dosage is:

- one 70 mg tablet once weekly

  or

- one bottle of 70 mg oral solution once weekly

  or

- one 10 mg tablet once daily

Prevention of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 35 mg tablet once weekly

  or

- one 5 mg tablet once daily

The safety of treatment and prevention of osteoporosis with FOSAMAX has been studied for up to 7 years.

Treatment of glucocorticoid-induced osteoporosis in men and women

The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

Paget's disease of bone in men and women

The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's disease

In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with FOSAMAX. Specific retreatment data are not available, although responses to FOSAMAX were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with FOSAMAX may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

HOW SUPPLIED

No. 3759 — Tablets FOSAMAX, 5 mg, are white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other. They are supplied as follows:

NDC 0006-0925-31 unit-of-use bottles of 30

NDC 0006-0925-58 unit-of-use bottles of 100.

No. 3797 — Tablets FOSAMAX, 10 mg, are white, oval, wax-polished tablets with code MRK on one side and 936 on the other. They are supplied as follows:

NDC 0006-0936-31 unit-of-use bottles of 30

NDC 0006-0936-58 unit-of-use bottles of 100

NDC 0006-0936-28 unit dose packages of 100

NDC 0006-0936-82 bottles of 1,000.

No. 3813 — Tablets FOSAMAX, 35 mg, are white, oval, uncoated tablets with code 77 on one side and a bone image on the other. They are supplied as follows:

NDC 0006-0077-44 unit-of-use blister package of 4

NDC 0006-0077-21 unit dose packages of 20.

No. 8457 — Tablets FOSAMAX, 40 mg, are white, triangular-shaped, uncoated tablets with code MSD 212 on one side and FOSAMAX on the other. They are supplied as follows:

NDC 0006-0212-31 unit-of-use bottles of 30.

No. 3814 — Tablets FOSAMAX, 70 mg, are white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the other. They are supplied as follows:

NDC 0006-0031-44 unit-of-use blister package of 4

NDC 0006-0031-21 unit dose packages of 20.

No. 3833 — Oral Solution FOSAMAX, 70 mg, is a clear, colorless solution with a raspberry flavor and is supplied as follows:

NDC 0006-3833-34 unit-of-use cartons of 4 single-dose bottles containing 75 mL each.

Storage

FOSAMAX Tablets:

Store in a well-closed container at room temperature, 15–30°C (59–86°F).

FOSAMAX Oral Solution:

Store at 25°C (77°F), excursions permitted to 15–30°C (59–86°F). [See USP Controlled Room Temperature.] Do not freeze.

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

FOSAMAX
(alendronate sodium) Tablets and Oral Solution

Issued January 2011

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[Exhibit 13 to Ecklund Declaration]

FDA U.S. Food and Drug Administration

Protecting and Promoting Your Health

Drugs

FDA Drug Safety Communication: Safety update for osteoporosis drugs, bisphosphonates, and atypical fractures

Safety Announcement

[10-13-2010] The U.S. Food and Drug Administration (FDA) is updating the public regarding information previously communicated describing the risk of atypical fractures of the thigh, known as subtrochanteric and diaphyseal femur fractures, in patients who take bisphosphonates for osteoporosis. This information will be added to the ***Warnings and Precautions*** section of the labels of all bisphosphonate drugs approved for the prevention or treatment of osteoporosis.

Bisphosphonates are a class of medicines that can be effective at preventing or slowing the loss of bone mass (osteoporosis) in postmenopausal women, thus reducing the risk of common osteoporotic bone fracture. Osteoporotic fractures can result in pain, hospitalization, and surgery.

Atypical subtrochanteric femur fractures are fractures in the bone just below the hip joint. Diaphyseal femur fractures occur in the long part of the thigh bone. These fractures are very uncommon and appear to account for less than 1% of all hip and

femur fractures overall. Although it is not clear if bisphosphonates are the cause, these unusual femur fractures have been predominantly reported in patients taking bisphosphonates.

The bisphosphonates affected by this notice are only those approved to treat osteoporosis, including Fosamax, Fosamax Plus D, Actonel, Actonel with Calcium, Boniva, Atelvia, and Reclast[1] (and their generic products).

This notice does not affect bisphosphonate drugs that only are used to treat Paget's disease or high blood calcium levels due to cancer (i.e., Didronel, Zometa, Skelid, and their generic products).

Although the optimal duration of bisphosphonate use for osteoporosis is unknown, these atypical fractures may be related to long-term term bisphosphonate use. FDA will require a new Limitations of Use statement in the *Indications and Usage* section of the labels for these drugs. This statement will describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis.

A Medication Guide will also be required to be given to patients when they pick up their bisphosphonate prescription. This Medication Guide will describe the symptoms of atypical femur fracture and recommend that patients notify their healthcare professional if they develop symptoms.

These actions are part of an ongoing safety review of bisphosphonate use and the occurrence of atypical subtrochanteric and diaphyseal femur fractures, as previously announced in a Drug Safety Communication on March 10, 2010[2].

Additional Information for Patients

If you currently take a bisphosphonate, you should:

- Continue to take your medication unless you are told to stop by your healthcare professional.
- Talk to your healthcare professional if you develop new hip or thigh pain (commonly described as dull or aching pain), or have any concerns with your medications.
- Report any side effects with your bisphosphonate medication to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals should:

- Be aware of the possible risk of atypical subtrochanteric and diaphyseal femur fractures in patients taking bisphosphonates.
- Continue to follow the recommendations in the drug label when prescribing bisphosphonates.
- Discuss the known benefits and potential risks of using bisphosphonates with patients.
- Evaluate any patient who presents with new thigh or groin pain to rule out a femoral fracture.
- Discontinue potent antiresorptive medications (including bisphosphonates) in patients who have evidence of a femoral shaft fracture.
- Consider periodic reevaluation of the need for continued bisphosphonate therapy, particularly

in patients who have been treated for over 5 years.

- Report any adverse events with the use of bisphosphonates to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Any information provided to MedWatch should be as detailed as possible and include information concerning fracture location/configuration, magnitude of trauma, fracture details (complete or incomplete, bilateral, or comminuted), presence and duration of prodromal thigh or groin pain, duration of bisphosphonate use, relevant medical history, and concomitant use of other medications.

Data Summary

FDA has reviewed all available data, including data summarized in the American Society for Bone and Mineral Research (ASBMR) Task Force report regarding bisphosphonates and atypical subtrochanteric and diaphyseal femur fractures[1], released on September 14, 2010. These atypical femur fractures can occur anywhere in the femoral shaft, from just below the lesser trochanter to above the supracondylar flare, and are transverse or short oblique in orientation without evidence of comminution. The fractures can be complete (involving both cortices) or incomplete (involving the lateral cortex only), and may be bilateral. Many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. The exact incidence of atypical femoral fractures is unknown but appears to account for less than one percent of hip and

femoral fractures overall. Therefore, atypical fractures are very uncommon. Although atypical femoral fractures have been predominantly reported in patients taking bisphosphonates, they have also been reported in patients who have not taken bisphosphonates.

The optimal duration of bisphosphonate treatment for osteoporosis is unknown. Bisphosphonate medications approved for the prevention and/or treatment of osteoporosis have clinical trial data supporting fracture reduction efficacy through at least 3 years of treatment and, in some cases, through 5 years. The FDA is continuing its evaluation of data supporting the safety and effectiveness of long term use (greater than 3 to 5 years) of bisphosphonates for the treatment and prevention of osteoporosis and will provide additional guidance at the completion of our review.

In summary, FDA is continuing its ongoing safety review of bisphosphonate use and the occurrence of atypical femur fractures. As of this notice, the FDA is notifying patients and healthcare professionals of new *Warnings and Precautions* information that is being added regarding this risk to the labels of all bisphosphonate products approved for the prevention or treatment of osteoporosis. A new Limitations of Use statement will describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis. In addition, the FDA will require that a Medication Guide be included with all bisphosphonate medications approved for osteoporosis indications to better inform patients of the risk for atypical femur fracture.

References:

1 Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American Society for Bone and Mineral Research [published online ahead of print]. *Journal of Bone and Mineral Research*. 2010; http://onlinelibrary.wiley.com/doi/10.1002/jbmr.253/pdf[3]. Accessed September 17, 2010.

Related Information

- Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa) Information[4]
- FDA Drug Safety Communication: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures[5]
- Possible Fracture Risk With Osteoporosis Drugs[6]
- FDA: Possible increased risk of thigh bone fracture with bisphosphonates[7] [ARCHIVED]
- Risk Evaluation and Mitigation Strategies (REMS) Letters to Sponsor/Applicants Requesting Labeling Changes[8]

Contact FDA

1-800-332-1088
1-800-FDA-0178 Fax
Report a Serious Problem

MedWatch Online[9]

Regular Mail: Use postage-paid FDA Form 3500[10]

Mail to: MedWatch 5600 Fishers Lane

Rockville, MD 20857

Page Last Updated: 10/14/2010

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Email FDA

[Exhibit 14 to Ecklund Declaration]

[redacted] 9635609
9636809

FOSAMAX ®

(ALENDRONATE SODIUM) TABLETS AND ORAL SOLUTION

DESCRIPTION

FOSAMAX (alendronate sodium) is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

The empirical formula of alendronate sodium is $C_4H_{12}NNaO_7P_2 \cdot 3H2O$ and its formula weight is 325.12. The structural formula is:

Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Tablets FOSAMAX for oral administration contain 6.53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. Tablets FOSAMAX 10 mg also contain carnauba wax.

Each bottle of the oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid. Each bottle also contains the following inactive ingredients: sodium citrate dihydrate and citric acid anhydrous as buffering agents, sodium saccharin, artificial raspberry flavor, and purified water. Added as preservatives are sodium propylparaben 0.0225% and sodium butylparaben 0.0075 %.

CLINICAL PHARMACOLOGY

Mechanism of Action

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere

* * *

- For the prevention of osteoporosis, FOSAMAX may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the

desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture.

Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of FOSAMAX for prevention of osteoporosis.

- Treatment to increase bone mass in men with osteoporosis
- Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density (see PRECAUTIONS, *Glucocorticoid-induced osteoporosis*). Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.
- Treatment of Paget's disease of bone in men and women
  - Treatment is indicated in patients with Paget's disease of bone having alkaline phosphatase at least two times the upper limit of normal, or those who are

symptomatic, or those at risk for future complications from their disease.

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes
- Patients at increased risk of aspiration should not receive FOSAMAX oral solution.
- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, *General*)

WARNINGS

FOSAMAX, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with FOSAMAX. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking FOSAMAX and/or who fail to swallow it with the recommended amount of water, and/or who continue to take FOSAMAX after developing

symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to mental disability, therapy with FOSAMAX should be used under appropriate supervision.

Because of possible irritant effects of FOSAMAX on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodenitis, or ulcers).

There have been post-marketing reports of gastric and duodenal ulcers, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

General

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FOSAMAX.

Presumably due to the effects of FOSAMAX on increasing bone mineral, small, asymptomatic

decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Musculoskeletal Pain

In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). This category of drugs includes FOSAMAX (alendronate). Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups.

Dental

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous

bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., pre-existing dental disease, anemia, coagulopathy, infection).

Patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy should receive care by an oral surgeon. Dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Renal insufficiency

FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Glucocorticoid-induced osteoporosis

The risk versus benefit of FOSAMAX for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see INDICATIONS AND USAGE). Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined FOSAMAX and glucocorticoid treatment.

The efficacy of FOSAMAX for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of FOSAMAX has been established in studies of two years' duration. The greatest increase in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of FOSAMAX beyond two years has not been studied.

The efficacy of FOSAMAX in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in postmenopausal women. The efficacy for prevention of non-vertebral fractures has not been demonstrated.

Information for Patients

General

Physicians should instruct their patients to read the patient package insert before starting therapy with FOSAMAX and to reread it each time the prescription is renewed.

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Dosing Instructions

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when it is

taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Absorption*).

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of FOSAMAX with a full glass of water (6–8 oz). To facilitate gastric emptying patients should drink at least 2 oz (a quarter of a cup) of water after taking FOSAMAX oral solution. Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking FOSAMAX and consult their physician.

Patients should be instructed that if they miss a dose of once weekly FOSAMAX, they should take one dose on the morning after they remember. They should not take two doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.

Drug Interactions (also see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Drug Interactions)*

Estrogen/hormone replacement therapy (HRT)

Concomitant use of HRT (estrogen ± progestin) and FOSAMAX was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence have not been studied (see CLINICAL PHARMACOLOGY, *Clinical Studies, Concomitant use with estrogen/hormone replacement therapy (HRT)* and ADVERSE REACTIONS, *Clinical Studies, Concomitant use with estrogen/hormone replacement therapy*).

Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of FOSAMAX. Therefore, patients must wait at least one-half hour after taking FOSAMAX before taking any other oral medications.

Aspirin

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of FOSAMAX greater than 10 mg and aspirin-containing products.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

FOSAMAX may be administered to patients taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking FOSAMAX 5 or 10mg/day compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with FOSAMAX.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2 The relevance of this finding to humans is unknown.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo*

chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (13 times a 40 mg human daily dose based on surface area, mg/m^2).

Pregnancy

Pregnancy Category C:

Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day

for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

There are no studies in pregnant women. FOSAMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSAMAX is administered to nursing women.

Pediatric Use

The efficacy and safety of FOSAMAX were examined in a randomized, double-blind, placebo-controlled two-year study of 139 pediatric patients, aged 4–18 years, with severe osteogenesis imperfect. One-hundred-and-nine patients were randomized to 5 mg FOSAMAX daily (weight <40 kg) or 10 mg FOSAMAX daily (weight ≥40 kg) and 30 patients to placebo. The mean baseline lumbar spine BMD Z-score of the patients was -4.5. The mean change in lumbar spine BMD Z-score from baseline to Month 24 was 1.3 in the FOSAMAX-treated patients and 0.1 in the placebo-treated patients. Treatment with FOSAMAX did not reduce the risk of fracture. Sixteen percent of the FOSAMAX patients who sustained a radiologically-confirmed fracture by Month 12 of the study had delayed fracture healing (callus remodeling) or fracture non-union when assessed radiographically at Month 24 compared with 9% of the placebo-treated patients. In FOSAMAX-treated patients, bone histomorphometry data obtained at Month 24 demonstrated decreased bone turnover and delayed mineralization time; however, there were no mineralization defects. There were no statistically significant differences between the FOSAMAX and placebo groups in reduction of bone pain.

FOSAMAX is not indicated for use in children.

(For clinical adverse experiences in children, see ADVERSE REACTIONS, *Clinical Studies, Osteogenesis Imperfecta.*)

Geriatric Use

Of the patients receiving FOSAMAX in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years

of age and 17% (n=550) were ≥75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 45%, 54%, 37%, and 70%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Clinical Studies

In clinical studies of up to five years in duration adverse experiences associated with FOSAMAX usually were mild, and generally did not require discontinuation of therapy.

FOSAMAX has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of osteoporosis

Postmenopausal women

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 years

and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: FOSAMAX, 3.2%; placebo, 2.7%. In these study populations, 49–54% had a history of gastrointestinal disorders at baseline and 54–89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX or placebo are presented in the following table.

* * *

Osteoporosis Prevention Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	Two/Three-Year Studies		One-Year Study	
	FOSAMAX 5 mg/day % (n=642)	Placebo % (n=648)	FOSAMAX 5 mg/day % (n=361)	Once Weekly FOSAMAX 35 mg % (n=362)
Gastrointestinal				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

Concomitant use with estrogen/hormone replacement therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with FOSAMAX 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Treatment of glucocorticoid-induced osteoporosis

In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX 5 or 10 mg/day or placebo are presented in the following table.

One-Year Studies in Glucocorticoid-Treated Patients Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients			
	FOSAMAX 10 mg/day % (n=157)	FOSAMAX 5 mg/day % (n=161)	Placebo % (n=159)
Gastrointestinal			
abdominal pain	3.2	1.9	0.0
acid regurgitation	2.5	1.9	1.3
constipation	1.3	0.6	0.0
melena	1.3	0.0	0.0
nausea	0.6	1.2	0.6
diarrhea	0.0	0.0	1.3
Nervous System/ Psychiatric			
headache	0.6	0.0	1.3

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year.

Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3–12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 1% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo.

Osteogenesis Imperfecta

FOSAMAX is not indicated for use in children.

The overall safety profile of FOSAMAX in OI patients treated for up to 24 months was generally similar to that of adults with osteoporosis treated with FOSAMAX. However, there was an increased occurrence of vomiting in OI patients treated with FOSAMAX compared to placebo. During the 24-month treatment period, vomiting was observed in 32 of 109 (29.4%) patients treated with FOSAMAX and 3 of 30 (10%) patients treated with placebo.

In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of FOSAMAX 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration. These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with an acute-phase response that has been reported in patients receiving bisphosphonates, including FOSAMAX. See

ADVERSE REACTIONS, *Post-Marketing Experience, Body as a Whole.*

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with FOSAMAX, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, *Information for Patients*, and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection,

often with delayed healing, has been reported rarely (see PRECAUTIONS, *Dental*).

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, *Musculoskeletal Pain*), joint swelling; low-energy femoral shaft and subtrochanteric fractures.

Nervous system: dizziness and vertigo.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m^2).

No specific information is available on the treatment of overdosage with FOSAMAX. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

FOSAMAX must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only (see PRECAUTIONS, *Information for Patients*). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of FOSAMAX (see PRECAUTIONS, *Drug Interactions*). Waiting less than 30 minutes, or taking FOSAMAX with food, beverages (other than plain water) or other medications will lessen the effect of FOSAMAX by decreasing its absorption into the body.

FOSAMAX should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, a FOSAMAX tablet should be swallowed with a full glass of water (6–8 oz). To facilitate gastric emptying FOSAMAX oral solution should be followed by at least 2 oz (a quarter of a cup) of water. Patients should not lie down for at least 30 minutes and until after their first food of the day. FOSAMAX should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see WARNINGS, PRECAUTIONS, *Information for Patients*).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see PRECAUTIONS, *General*).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX is not recommended for patients with more severe renal

insufficiency (creatinine clearance <35 mL/min) due to lack of experience.

Treatment of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 70 mg tablet once weekly

  or

- one bottle of 70 mg oral solution once weekly

  or

- one 10 mg tablet once daily

Treatment to increase bone mass in men with osteoporosis

The recommended dosage is:

- one 70 mg tablet once weekly

  or

- one bottle of 70 mg oral solution once weekly

  or

- one 10 mg tablet once daily

Prevention of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 35 mg tablet once weekly

  or

- one 5 mg tablet once daily

The safely of treatment and prevention of osteoporosis with FOSAMAX has been studied for up to 7 years.

Treatment of glucocorticoid-induced osteoporosis in men and women

The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

Paget's disease of bone in men and women

The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's disease

In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with FOSAMAX. Specific retreatment data are not available, although responses to FOSAMAX were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with FOSAMAX may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

HOW SUPPLIED

No. 3750 — Tablets FOSAMAX, 5 mg, are white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other. They are supplied as follows:

NDC 0006-0925-31 unit-of-use bottles of 30

NDC 0006-0925-58 unit-of-use bottles of 100.

No. 3797 — Tablets **FOSAMAX**, 10 mg, are white, oval, wax-polished tablets with code **MRK** on one side and 936 on the other. They are supplied as follows:

NDC 0006-0936-31 unit-of-use bottles of 30

NDC 0006-0936-58 unit-of-use bottles of 100

NDC 0006-0936-28 unit dose packages of 100

NDC 0006-0936-82 bottles of 1,000.

No. 3813 — Tablets **FOSAMAX**, 35 mg, are white, oval, uncoated tablets with code 77 on one side and a bone image on the other. They are supplied as follows:

NDC 0006-0077-44 unit-of-use blister package of 4

NDC 0006-0077-21 unit dose packages of 20.

No. 8457 — Tablets **FOSAMAX**, 40 mg, are white, triangular-shaped, uncoated tablets with code MSD 212 on one side and FOSAMAX on the other. They are supplied as follows:

NDC 0006-0212-31 unit-of-use bottles of 30.

No. 3814 — Tablets **FOSAMAX**, 70 mg, are white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the other. They are supplied as follows:

NDC 0006-0031-44 unit-of-use blister package of 4

NDC 0006-0031-21 unit dose packages of 20.

No. 3833 — Oral Solution **FOSAMAX**, 70 mg, is a clear, colorless solution with a raspberry flavor and is supplied as follows:

NDC 0006-3833-34 unit-of-use cartons of 4 single-dose bottles containing 75 mL each.

Storage

FOSAMAX Tablets:

Store in a well-closed container at room temperature, 15–30°C (59–86°F).

FOSAMAX Oral Solution:

Store at 25°C (77°F), excursions permitted to 15–30°C (59–86°F). [See USP Controlled Room Temperature.] Do not freeze.

MERCK & CO., INC.

Whitehouse Station, NJ 08889, USA

Issued June 2009
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[Exhibit 15 to Ecklund Declaration]

* * *

response for the team review by July 7th. Please let me know if you have any concerns regarding the timeline.

Jim

From: Marchick, Julie
[mailto:Julie.Marchick @fda.hhs.gov]
Sent: Friday, June 13, 2008 12:24 PM
To: Adams, James H (WRG)
Subject: Fosamax Information Request - Atypical Fractures

Jim,

We are aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates (1–5). The subtrochanteric type of hip or femoral fracture is reportedly rare in patients with osteoporosis not on bisphosphonates. We are concerned about this developing safety signal. Please submit any investigations that you have conducted regarding the occurrence of atypical fractures with bisphosphonate use as well as any investigational plans. Please submit all hip and femoral fracture case reports you have received. Where possible, efforts should be made to clarify the fracture location and the duration of bisphosphonate exposure for all case reports.

We request a written response by Friday, July 11, 2008.

Please contact me if you have any questions.

Thanks,

Julie

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Food and Drug Administration
301 -796-1280 (phone)
301 -796-9712 (fax)
julie.marchick@fda.hhs.gov

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fragility. J Clin Endocrinol Metab. 2008 epublished ahead of print 6/3/2008.

[Exhibit 21 to Ecklund Declaration]

PERSPECTIVE JBMR

Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research

Elizabeth Shane,* David Burr,* Peter R Ebeling, Bo Abrahamsen, Robert A Adler, Thomas D Brown, Angela M Cheung, Felicia Cosman, Jeffrey R Curtis, Richard Dell, David Dempster, Thomas A Einhorn, Harry K Genant, Piet Geusens, Klaus Klaushofer, Kenneth Koval, Joseph M Lane, Fergus McKiernan, Ross McKinney, Alvin Ng, Jeri Nieves, Regis O'Keefe, Socrates Papapoulos, Howe Tet Sen, Marjolein CH van der Meulen, Robert S Weinstein, and Michael Whyte

Author affiliations appear on pp. 2288–2289

ABSTRACT

Reports linking long-term use of bisphosphonates (BPs) with atypical fractures of the femur led the leadership of the American Society for Bone and Mineral Research (ASBMR) to appoint a task force to address key questions related to this problem. A multidisciplinary expert group reviewed pertinent published reports concerning atypical femur fractures, as well as preclinical studies that could provide insight into their pathogenesis. A case definition was developed so that subsequent studies report on the same condition. The task force defined major and minor features of complete and incomplete atypical femoral fractures and recommends that all major

features, including their location in the subtrochanteric region and femoral shaft, transverse or short oblique orientation, minimal or no associated trauma, a medial spike when the fracture is complete, and absence of comminution, be present to designate a femoral fracture as atypical. Minor features include their association with cortical thickening, a periosteal reaction of the lateral cortex, prodromal pain, bilaterality, delayed healing, comorbid conditions, and concomitant drug exposures, including BPs, other antiresorptive agents, glucocorticoids, and proton pump inhibitors. Preclinical data evaluating the effects of BPs on collagen cross-linking and maturation, accumulation of microdamage and advanced glycation end products, mineralization, remodeling, vascularity, and angiogenesis lend biologic plausibility to a potential association with long-term BP use. Based on published and unpublished data and the widespread use of BPs, the incidence of atypical femoral fractures associated with BP therapy for osteoporosis appears to be very low, particularly compared with the number of vertebral, hip, and other fractures that are prevented by BPs. Moreover, a causal association between BPs and atypical fractures has not been established. However, recent observations suggest that the risk rises with increasing duration of exposure, and there is concern that lack of awareness and underreporting may mask the true incidence of the problem. Given the relative rarity of atypical femoral fractures, the task force recommends that specific diagnostic and procedural codes be created and that an international registry be established to facilitate studies of the clinical and genetic risk factors and optimal surgical and medical

management of these fractures. Physicians and patients should be made aware of the possibility of atypical femoral fractures and of the potential for bilaterality through a change in labeling of BPs. Research directions should include development of animal models, increased surveillance, and additional epidemiologic and clinical data to establish the true incidence of and risk factors for this condition and to inform orthopedic and medical management.

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KEY WORDS: OSTEOPOROSIS; BONE; PAIN; FRACTURE; ATYPICAL; SUBTROCHANTERIC; FEMORAL DIAPHYSIS; BISPHOSPHONATES

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Introduction

Reports of atypical femoral fractures, predominantly in patients receiving long-term bisphosphonates (BPs), led the leadership of the American Society for Bone and Mineral Research (ASBMR) to appoint a task force to address a number of key questions related to this disorder. Specifically, the task force was asked to

1. Make a recommendation for a provisional case definition of atypical femoral fractures so that subsequent studies report on the same condition.
2. Review carefully the currently available information in order to assess what is actually known and what is not known about atypical femoral fractures and their potential relationship with BP usage.
3. Recommend the development of noninvasive diagnostic and imaging techniques with which to better characterize and diagnose the disorder.
4. Identify the key questions that the scientific community should address and recommend a research agenda to elucidate incidence, pathophysiology, and etiology of atypical femoral

fractures and their potential relationship with BP usage.

5. Recommend clinical orthopedic and medical management of atypical femoral fractures based on available information.

This report summarizes the findings and recommendations of the task force.

Methods

The expert committee

The expert committee consisted of an international multidisciplinary group of 28 individuals with expertise in clinical and basic bone biology, endocrinology, epidemiology, radiology, biomechanics, and orthopedic surgery. The expert committee also included a basic scientist (TDB) working in the bone field but not in the areas of osteoporosis and BPs and a physician and bioethicist (RM) with expertise in conflict issues affecting biomedical researchers.

Review of the literature/data acquisition

A literature search using PubMed and OVID sought English-language articles with full text abstracts during the period January 1990 to April 30, 2010. The search terms specified included *atypical fracture, subtrochanteric fracture, femoral fracture, diaphyseal fracture, shaft fracture, cortical fracture, bilateral fracture, transverse fracture, low-energy fracture, spontaneous fracture, insufficiency fracture, stress fracture, bisphosphonates, antiresorptive, bone turnover, alendronate, pamidronate, etidronate, ibandronate, risedronate, zoledronate, zoledronic acid, Didronel, Actonel, Fosamax, Reclast,* and *Boniva.* The abstracts retrieved were reviewed by one coauthor

(PRE) to assess their relevance to atypical fractures or long-term complications of BPs, and full text articles of each abstract selected were reviewed subsequently by four members of the ASBMR task force in order to construct the relevant sections of this article. The numbers of subjects in each study; the age and sex of subjects; the specific BP(s) used (if any); the dose and duration of BP exposure; the clinical presentation; a prodrome of pain; the characteristics of the reported fracture(s); the level of trauma; the presence of either bilateral fractures or bilateral radiologic changes and comorbid conditions such as rheumatoid arthritis (RA) and diabetes (DM); the concomitant use of other antiresorptive drugs, glucocorticoids (GCs), or proton pump inhibitors (PPIs); the presence of vitamin D deficiency (<20 ng/ mL); the presence of a bone mineral density (BMD) *T*-score greater than –2.5 (osteopenia or normal BMD); information on bone histology; management and outcome; and any other information were included, when available. Identification of case duplication between studies was achieved by cross-referencing studies whenever possible. The anatomic regions and locations of hip fractures are illustrated in Fig. 1.

Results and Discussion

Make a recommendation for a provisional case definition of atypical femoral fractures so that subsequent studies report on the same condition

Atypical femoral fractures are observed most commonly in the proximal one-third of the femoral shaft but may occur anywhere along the femoral diaphysis from just distal to the lesser trochanter to proximal to the supracondylar flare of the distal

femoral metaphysis. The fracture usually occurs as a result of no or minimal trauma, equivalent to a fall from a standing height or less. The fracture may be complete, extending across the entire femoral shaft, often with the formation of a medial spike (Fig. 2*A*). Complete atypical femoral fractures generally are transverse, although they may have a short oblique configuration, and are not comminuted. Alternatively, the fracture may be incomplete, manifested by a transverse radiolucent line in the lateral cortex. Both complete and incomplete fractures are commonly associated with a periosteal stress reaction and thickening of the lateral cortex at the fracture site (Fig. 2*B*), abnormalities indicative of a stress fracture. In addition, there may be generalized bilateral thickening of both the medial and lateral cortices. Either complete or incomplete atypical fractures may be bilateral. Healing of the fractures may be delayed. There are often prodromal symptoms such as a pain in the groin or thigh. Atypical fractures may be associated with a variety of comorbid conditions and the use of pharmaceutical agents. The diagnosis of atypical femoral fractures should specifically exclude fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with local primary or metastatic bone tumors, and periprosthetic fractures.

Fig. 1. Locations of common hip and femur fractures. (*Courtesy of Thomas Einhorn, MD.*)

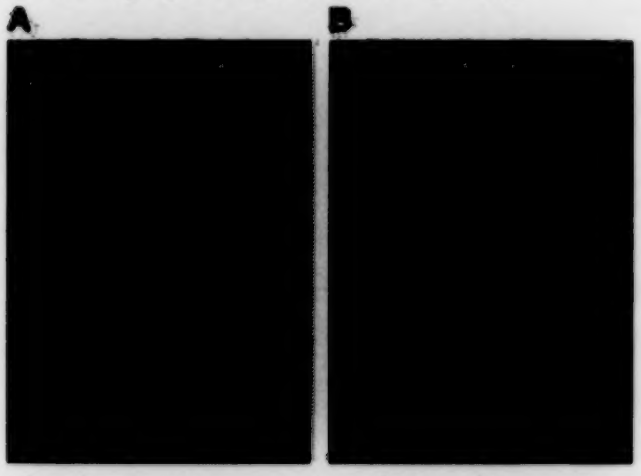

Fig. 2. Anteroposterior (AP) radiographs showing an atypical femoral shaft fracture (*A*) pre- and (*B*) postoperatively from the same individual. Note the oblique and transverse components (*white arrows*) and a medial "spike" (*black arrow*) on the preoperative

view and the lateral, transverse, lucent fracture line and associated focal cortical thickening with a "beaked" appearance (*arrow*) on the postoperative view. (*Courtesy of Thomas Einhorn, MD.*)

To assist in case finding and reporting, the task force defined major and minor features for complete and incomplete atypical fractures of the femur (Table 1). All major features should be present in order to designate a fracture as atypical and distinguish it from more common hip fractures (ie, femoral neck, intertrochanteric). Minor features commonly have been described in association with atypical fractures but may or may not be present in individual patients. Although atypical femoral fractures have been reported most prominently in individuals who have been treated with BPs, such fractures have been reported in individuals with no history of BP exposure. Therefore, to facilitate studies comparing the frequency of atypical femoral fractures in patients with and without BP therapy, association with BP therapy was included as a minor feature.

Review carefully the currently available information in order to assess what is actually known and what is not known about atypical femoral fractures and their potential relationship with BP usage

The task force recognized that the incidence of atypical femoral fractures has come to medical attention principally in the setting of BP use and that the incidence in the general population not exposed to BPs is unknown. Although the association between BP use and atypical femoral fractures is consistent

with a role for BPs, they have not been proven to be causal. To address this charge, the task force considered both preclinical and epidemiologic data, reviewed all case reports and series of atypical femoral fractures, and conducted interviews with physician and scientist representatives of pharmaceutical companies that market drugs for osteoporosis and the US Food and Drug Administration (USFDA).

Table 1. Atypical Femoral Fracture: Major and Minor Features[a]

Major features[b]

- Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
- Associated with no trauma or minimal trauma, as in a fall from a standing height or less
- Transverse or short oblique configuration
- Noncomminuted
- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.

Minor features

- Localized periosteal reaction of the lateral cortex[c]
- Generalized increase in cortical thickness of the diaphysis
- Prodromal symptoms such as dull or aching pain in the groin or thigh
- Bilateral fractures and symptoms
- Delayed healing

- Comorbid conditions (eg, vitamin D deficiency, RA, hypophosphatasia)
- Use of pharmaceutical agents (eg, BPs, GCs, PPIs)

[a]Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic bone tumors, and periprosthetic fractures.

[b]All major features are required to satisfy the case definition of atypical femoral fracture. None of the minor features are required but sometimes have been associated with these fractures.

[c]Often referred to in the literature as *beaking* or *flaring*.

Insights into the pathogenesis of atypical femoral fractures from basic studies

The radiologic presentation of atypical femoral fractures bears striking similarities to that of stress fractures[1] and also may resemble that of pseudofractures.[2] About 70% of patients with a confirmed stress fracture of the femur report prodromal pain for a period of weeks before the diagnosis. Radiographic features of stress fractures typically include a periosteal callus that appears hazy and indistinct initially and later solidifies. The periosteal callus is clear evidence of an attempt at repair prior to overt fracture and also occurs in atypical femoral fractures adjacent to the evolving fracture on the lateral cortex (Fig. 2*B*). Rats,[3,4] rabbits,[5,6] dogs,[7] and horses[8,9] all have been used to

study stress fractures and, because of the similarities between stress fractures and atypical femoral fractures, could be useful models to study the pathogenesis of atypical femoral fractures.

Patients with atypical femoral fractures often also have a more generalized thickening of both the medial and lateral cortices bilaterally. This may be a normal genetically determined variant of femoral shape but has been observed often in those who have sustained an atypical femoral fracture. However, there is no evidence that BPs are associated with this more generalized cortical thickening because they are not known to stimulate periosteal apposition, nor do their antiremodeling effects lead to enhanced endosteal formation.

Atypical femoral fractures in patients on BPs have occurred in the setting of comorbid conditions with known adverse effects on bone quality (eg, DM).[10–13] A relatively large proportion of patients also has taken GCs in addition to BPs. GCs reduce osteoblast activity, increase osteoblast apoptosis,[14–16] and are also associated with osteonecrosis of the femoral head.[14,17] In DM, high glucose levels cause the accumulation of advanced glycation end products (AGEs) that have been associated with an increased risk of fracture.[18] In vitro[19] and in vivo studies[20,21] demonstrate that AGE accumulation increases the brittleness of bone.

BP effects on collagen. The organic matrix is the principal determinant of toughness, a measure of the intrinsic energy–absorption capacity of bone.[22–24] Bone collagen contains both enzymatic and nonenzymatic collagen cross-links; both stabilize the matrix and have significant impact on the bone's

mechanical properties. Enzymatic cross-links are first formed as immature divalent cross-links that are eventually converted to mature trivalent cross-links, pyridinoline (PYD), deoxypyridinoline (DPD), and pyrroles. Nonenzymatic cross-links are formed through the interaction of collagen and sugars via oxidation reactions. They are associated with the accumulation of AGEs in bone.

BPs are associated with both positive and negative effects on bone's organic matrix by altering both collagen maturity and cross-linking. Following 1 year of treatment with a wide range of BP doses, the PYD/DPD ratio was increased significantly in vertebral cancellous bone and tibial cortical bone from BP–treated dogs compared with untreated controls.[20,21] An increased PYD/DPD ratio has been associated with increased strength and stiffness of bone,[25,26] and subsequent mechanical analyses of vertebrae confirmed this in dogs. However, reducing bone turnover also increases pentosidine levels, a marker for AGEs. AGEs are associated with tissue that is more brittle[25] and cause reductions in postyield deformation,[19,26] energy to fracture,[21,27] and toughness.[20] Indeed, tissue from both vertebral[28] and tibial[21] bone from BP-treated animals was less tough than bone from animals not treated with BPs. Pentosidine levels also were increased in the ribs of dogs after 3 years of treatment with incadronate.[29] However, caution should be exercised when interpreting the results of these studies because they involved BP administration to normal rather than osteoporotic dogs.

There are limited data on collagen cross-links in humans treated with BPs. Using Fourier-transformed

infrared spectroscopy (FTIR), Durchschlag and colleagues[30] showed that BP treatment prevented the maturation of collagen found in patients not treated with BPs and reduced collagen maturity in newly formed bone. Boskey and colleagues[31] reported no change in collagen maturity in women treated with alendronate. Donnelly and colleagues[32] showed similar mean values but a narrowed distribution of collagen maturity and enzymatic crosslinks in a small number of women with common proximal femoral fractures without features of atypia who had been treated with BPs for an average of 7 years.

BP effects on bone mineralization density distribution (BMDD). BMDD is a measure of the degree and heterogeneity of mineralization in bone tissue.[33–35] In the healthy adult population, BMDD of cancellous bone shows only minor variations with age, gender, ethnicity, and skeletal site,[36] indicating that the normal BMDD corresponds to a biologic and mechanical optimum. Therefore, even small deviations from the normal BMDD may have biologic meaning. Because the effectiveness of bone in stopping cracks is directly proportional to the stiffness ratio across its internal interfaces, a homogeneous material will be less effective in slowing or stopping cracks initiated in the bone matrix, permitting cracks to grow more quickly to critical size and ultimately increase fracture risk.[37]

BP treatment reduces bone turnover, increases overall mineralization, but leaves mineral particle shape, thickness, and orientation unaffected, narrows the BMDD, and increases bone strength and stiffness.[33,34] BP effects on BMDD have been studied only in transiliac bone biopsies, so there is limited

knowledge about their effects on cortical bone from other sites. However, Donnelly and colleagues[38,39] have shown that the range of mineral distribution at the proximal femur is significantly narrower than that in the iliac crest and that postmenopausal women treated with BPs for an average of 8 years demonstrated substantially less tissue heterogeneity in terms of mineralization, crystal size, and crystal perfection than those who had not been treated. Cortical tissue seemed to be affected preferentially. Narrowing of the BMDD by BPs may be transient. After 5 to 10 years of BP treatment, BMDD was restored to within the normal premenopausal range.[40–43]

Effects of reducing remodeling on microdamage accumulation. Excessive bone remodeling results in microarchitectural deterioration and consequent loss of bone mass and strength and increased susceptibility to fragility fractures. BPs increase bone strength and decrease fracture risk by suppressing excessive bone remodeling. Reduction of remodeling, however, is also associated with increased microdamage accumulation because cracks are not removed efficiently. Even in the absence of BP treatment, age-related reductions in bone turnover result in microdamage accumulation.[28] There is a threefold increase in damage accumulation in the vertebrae of dogs between 2 and 5 years of age that is associated with a 50% reduction in turnover.[28] Damage also accumulates significantly in humans with age, particularly after the age of 70 years,[44,45] although there is broad interindividual variability in the amount. BPs may exacerbate damage accumulation because they impair targeted remodeling to a greater extent than remodeling not

targeted to damage repair (ie, stochastic remodeling),[46,47] thereby allowing microdamage to persist for longer compared with untreated bone. This accumulation of damage is nonlinear and increases more quickly the more that remodeling is suppressed.[48] However, marked reduction of turnover is not necessary to induce a significant accumulation of microdamage. Reducing trabecular bone activation frequency in the canine vertebra by approximately 40% with risedronate is associated with a threefold increase in microdamage compared with untreated controls,[48] and suppression by approximately 20% with raloxifene is associated with a doubling of microdamage.[49]

Studies of iliac crest biopsies provide conflicting data about whether microdamage accumulates with BP treatment in humans. One study that evaluated women treated for an average of 5 years with alendronate showed significant microcrack accumulation in a subsample, but the study is inconclusive because the analyses of biopsies from the two different clinical sites associated with the study differed.[50] A second study did not find an association between BP treatment and damage accumulation in the iliac crest.[51] Neither study evaluated samples from the femoral cortex, and because the accumulation of microdamage is site-specific, it is unknown whether damage accumulates in the cortex of the femoral diaphysis.

Effects of reducing remodeling on tissue mechanical properties. Not only is microdamage accumulation with BP treatment a function of reduced repair, but BP-treated bone also is more susceptible to increased crack initiation,[52] perhaps because AGE

accumulation causes bone tissue to become more brittle. In one study, dogs were treated for 1 year with either risedronate or alendronate at doses equivalent to those used to treat postmenopausal osteoporosis.[52] Vertebrae then were removed and loaded cyclically in compression (5 Hz for 100,000 cycles at loads ranging from 100% to 300% of body weight); cracks were significantly more likely to initiate, but not necessarily to grow, in bone treated with alendronate than in those treated either with risedronate or with saline.[52]

Preclinical studies show that treatment with BPs is associated with reduced bone toughness.[48,53,54] Following 1 to 3 years of BP treatment at doses similar to or greater than those used in postmenopausal women, toughness was 20% to 30% lower than in control animals.[48,53] It was thought initially that the decline in toughness was related to the well-documented accumulation of microdamage that was observed in lumbar vertebrae and other bones of dogs treated with BPs,[48,54,55] although changes to both mineralization and collagen cross-linking also occur. More recent data show that toughness continues to decline in animals with long-term BP treatment without an increase in micro–damage accumulation or a further increase in secondary mineralization.[28] In a 1-year study using various doses of alendronate or risedronate, there was minimal correspondence between changes in micro-damage accumulation and material-level toughness in vertebrae from several groups of BP-treated dogs.[48] Likewise, animals not treated with BPs have an age-related threefold increase in microdamage accumulation without a change in bone toughness.[28] These lines of evidence suggest that neither microdamage nor increased

secondary mineralization is solely responsible for the change in bone material properties with BP therapy, leaving changes in collagen or interactions among all these properties as likely reasons for the progressive decline in toughness. However, the evidence also suggests that decreased remodeling is not solely responsible for reduced toughness, implicating a specific effect of BPs that is independent of reduced turnover.

The mechanical effect of BPs to decrease tissue toughness is countered by their capacity to increase bone mass and mineralization, promote collagen matrix maturation, and prevent microarchitectural deterioration of bone. These factors lead to increases in bone strength and stiffness that offset reduced toughness and make bone stronger at the structural level.

Affinity and retention of BPs in bone. The high affinity of BPs for bone mineral[56] and their long-term retention in bone[57] are of some concern because continued accumulation of BPs or persistent reduction of remodeling for prolonged treatment periods eventually could increase the risk of fracture, even in the face of increased bone mass. However, the toughness of the femoral diaphysis in nonosteoporotic dogs treated for as long as 3 years was not reduced, even with high doses of alendronate.[58] Moreover, cortical thickening, a feature of atypical femoral fractures, was not detected. In the absence of estrogen deficiency, the turnover rate in cortical bone has been estimated at approximately 3% per year,[59] based on biopsies from the rib, which is known to have a relatively high rate of turnover compared with other cortical bone sites. This is about one-tenth the rate of

turnover in cancellous bone.[59] The turnover rate of the femoral diaphysis is undoubtedly even slower than cortical bone from the rib. In 5-year-old beagle dogs, which have cortical bone that is structurally very similar to human bone, the rate of turnover in the femoral cortex is about 1% per year,[58] very much like that found in cortical bone from the femoral neck.[60] While this slow turnover makes the possibility of oversuppression of cortical bone remodeling in the femur unlikely, it is possible that prolonged reduction of remodeling could have an additive effect over time, especially if BPs continue to accumulate in the tissue. This may be relevant to atypical femoral fractures, where case series suggest a potentially significant effect of duration of treatment and a median treatment period of 5 years, according to Giusti and colleagues,[11] and 7 years, according to the current review.

Effects of BPs on fracture healing. Stress fractures and acute fractures of long bones heal by different mechanisms. Complete fractures heal via endochondral ossification, with an initial inflammatory response and the formation of a cartilage callus. BPs do not impair the initial phases of fracture healing or the development of a proliferative callus.[61–63] They only slow the remodeling phase, delaying the remodeling of the calcified cartilage callus to mature bone. In contrast, stress fractures heal by normal bone remodeling, which is reduced by BP treatment. BPs in the form of technetium-99m are used for bone scintigraphy and localize at sites of high bone turnover, microdamage, and fractures.[1,64] The localization of BPs at sites of stress injury would not affect periosteal callus

formation but could compromise intracortical bone repair of the damage itself by lowering the activation of new remodeling even further. Consistent with this hypothesis, treatment with BPs during military training did not lower the risk for stress fractures.[65] Animal studies using repetitive ulnar loading in combination with BP treatment also show that prior alendronate treatment does not protect against a fatigue-related reduction in mechanical properties.[66] However, prior alendronate treatment did eliminate the adaptive remodeling response, suggesting that BP treatment could impair the healing response to a stress fracture. Therefore, it is possible that in the case of a developing stress fracture, reduction of bone remodeling would prevent or delay the repair of the stress reaction without suppressing the appearance of a periosteal callus and that this may result eventually in consolidation of the damage and a complete fracture of the stressed site.

Effects of BPs on angiogenesis. The effects of BPs on stress fracture repair could be exacerbated if BPs are also antiangiogenic. The periosteum of the femoral shaft is thick and highly vascularized.[67] An effective stress fracture healing response requires an increase in periosteal vascularity. Although some observations identify a direct suppression of vasculogenesis by BPs,[68] it can be difficult in bone to distinguish between inhibition of new vessel growth and suppression of osteoclastic activity because both are coupled. However, dissociation between the two is possible during skeletal development in animal models, and studies of growing animals showed no antiangiogenic effect of clodronate.[69] Still, primary studies in nonskeletal tissues suggest that

angiogenesis indeed may be reduced by BPs over and above the normal reduction that would occur because of the absence of effective osteoclastic tunneling.[70] Interestingly, in a rat model of stress fracture, there is upregulation of vascular endothelial growth factor (VEGF) mRNA within 1 to 4 hours of initiation of the stress fracture[71,72] and upregulation of osteogenic genes in the cambium layer of the periosteum within 3 days. Early upregulation of interleukin 6 (IL-6) and IL-11 suggest the importance of remodeling in stress fracture healing.[72] These responses may well be coordinated, and any agent that suppresses angiogenesis could inhibit the repair of an impending stress fracture.

Summary of preclinical studies. The preclinical data provide a mixed picture of the effects of BPs on bone's matrix composition and mechanical properties. BPs reduce bone remodeling, preventing the loss of bone and deterioration of cancellous microarchitecture that accompany it. By reducing the number of new remodeling sites, BPs increase bone density, mineralization, and strength. Increases in fully mature collagen cross-links further contribute to the increased strength and stiffness associated with these other changes. However, at the same time, lowering of remodeling by BPs allows the accumulation of microdamage and increases the formation of AGEs, both of which reduce tissue toughness or the energy-absorbing capacity of bone tissue. Reduced remodeling also increases the homogeneity of the bone tissue, which could permit further damage accumulation, although this effect may be transient and not associated with long-term BP use. However, changes that reduce energy-absorbing capacity may be

particularly significant if a person sustains a low-energy impact such as a fall. Reduced remodeling may impair the healing of a stress fracture without altering the callus bridging that is the adaptation to and accompanies the stress fracture itself. Reduced angiogenesis would contribute to this delay in healing. While the preclinical studies reviewed here provide some insights regarding the possible pathogenesis of atypical femoral fractures, additional studies are required to identify potential pathogenic mechanisms that involve pathologic changes to bone matrix (Table 2), and animal models that more accurately mimic atypical fractures need to be developed.

Epidemiology of Subtrochanteric and Femoral Shaft Fractures

General epidemiology of subtrochanteric and femoral shaft fractures. Fractures located in the subtrochanteric region or femoral shaft (diaphysis) account for 7% to 10% of all hip/femoral diaphyseal fractures.[73,74] Approximately 75% of complete subtrochanteric and femoral shaft fractures are associated with major trauma such as motor vehicle accidents,[73] in which the energy transmitted to the bone results in the propagation of multiple fracture lines, thus producing comminution. Especially in older patients, femoral shaft fractures may occur below the stem of the prosthesis after total hip replacement.[75] In adults of all ages, more than half of femoral shaft fractures are spiral fractures, with the remainder presenting with a transverse or oblique configuration.[73,76]

Subtrochanteric fractures have important effects on mortality and morbidity. A study of 87 patients with

subtrochanteric fractures showed a mortality rate of 14% at 12 months and 25% at 24 months. Moreover, by 24 months, almost half had not achieved their prefracture functioning in terms of walking and performing other activities of daily living. In addition, many (71%) were unable to live in conditions similar to those before the fracture.[77] These outcomes are similar to long-term outcomes for people with femoral neck fractures.[78–81]

Table 2. Possible Pathogenetic Mechanisms Associated With Atypical Subtrochanteric Femoral Fractures

- Alterations to the normal pattern of collagen cross-linking
  - Changes to maturity of cross-links formed by enzymatic processes
  - Advanced glycation end-product accumulation
- Microdamage accumulation
- Increased mineralization
- Reduced heterogeneity of mineralization
- Variations in rates of bone turnover
- Reduced vascularity and antiangiogenic effects

A comprehensive review of 6409 femoral shaft fractures in Swedish inpatients showed a bimodal age distribution of incidence in both males and females,[82] similar to that reported by Singer and colleagues.[83] The age-specific incidence rates (per 100,000) for subtrochanteric fractures increased between the 65– and 85– year categories in both males and females in

Iran,[84] in the United States,[85] and in the United Kingdom.[86] Although femoral shaft fractures were more common among males than among females up to age 49, this gender difference was reversed in the 60– to 69– year age group.[82] Thus subtrochanteric fractures share features of typical osteoporosis-related fractures, including (1) higher incidence among women than among men, (2) a steep increase in incidence with age, and (3) more common occurrence in the elderly after low-energy trauma.[82,87–89] The number of admissions for femoral shaft fractures was unchanged from 1998 to 2004 in Sweden[82] and from 1996 to 2006 in the United States.[74]

The epidemiology of femoral neck and trochanteric and intertrochanteric hip fractures was compared with that of subtrochanteric and femoral shaft fractures in the United States among people 50 years of age and older using both the National Hospital Discharge Survey from 1996 to 2006 and MarketScan, a large medical claims database, from 2002 to 2006.[74] In women, hospital discharge rates of hip fracture (femoral neck and trochanteric and intertrochanteric regions) decreased from about 600 per 100,000 to 400 per 100,000 person-years in the decade after 1996. In contrast, subtrochanteric and femoral shaft fracture rates did not change, with an annual incidence of less than 30 per 100,000 person-years.[74] These findings confirmed that hip fracture incidence has declined since BPs were approved for use, whereas subtrochanteric and femoral shaft fractures have remained stable. Another US study of hospitalizations between 1996 and 2007 for hip (ie, femoral neck, intertrochanteric) and subtrochanteric fractures confirmed that femoral neck/intertrochanteric

fractures declined by 12.8% (263,623 in 1996 to 229,942 in 2007).[90] However, in contrast to the study by Nieves and colleagues,[74] subtrochanteric fractures increased from 8273 to 10,853 over the same period.[90] Neither study could ascertain specific radiologic features of atypia discussed in the case series.[74,90]

Recent data from the Study of Osteoporotic Fractures (SOF), a prospective population-based US study of 9704 white women 65 years of age and older followed for as long as 24 years indicate that the incidence of subtrochanteric fractures is very low (3 per 10,000 person-years) compared with the overall incidence of hip fracture (103 per 10,000 person-years).[91] After excluding high–energy, pathologic, and periprosthetic fractures, 48 subtrochanteric fractures occurred in 45 women (3.4% of hip fractures), 9 of whom received BPs. Predictors of subtrochanteric hip fracture were older age, lower total hip BMD, and a history of falls. In multivariate models, only increasing age remained significant. Predictors of femoral neck fracture were similar in this largely BP–naive group. Since fracture radiographs were not available, features of atypia were not ascertained. However, in 33 of the 45 women from the SOF with subtrochanteric fractures, baseline pelvis radiographs were available. When compared with 388 randomly selected controls, women with the thickest medial femoral shaft cortices were at lower risk of subtrochanteric and femoral neck fracture than those with the thinnest cortices.[92] Although lateral cortical thickening is described commonly in patients with atypical fractures, thickness of the lateral cortex was not related to fracture risk. Since only 6 women in the subset with pelvic radiographs had taken BPs, more

data are required on the role of cortical thickness in atypical femoral fractures in BP users.

Subtrochanteric and femoral shaft fractures and BP use. In a retrospective case-control study of postmenopausal women,[93] 41 cases of low-trauma subtrochanteric and femoral shaft fractures were identified and matched by age, race, and body mass index (BMI) to one intertrochanteric and one femoral neck fracture patient who presented during the same time period (2000–2007). BP use was documented in 15 of the 41 (37%) subtrochanteric and femoral shaft fracture patients compared with 9 of the 82 (11%) intertrochanteric and femoral neck fracture patients, resulting in an odds ratio (OR) of 4.44 [95% confidence interval (CI) 1.77–11.35]. Long-term BP use was more likely and duration of BP use was longer in subtrochanteric and femoral shaft fracture patients than in both hip fracture control groups ($p = .001$). Radiographs showed fractures with a transverse or oblique orientation, cortical thickening, and localized diffuse bone formation on the lateral cortex in 10 of the 15 fracture patients on a BP and in 3 of 26 fracture patients who were not taking a BP (OR = 15.33, 95% CI 3.06–76.90, $p < .001$).

In a cross-sectional study of 11,944 Danish people over age 60, Abrahamsen and colleagues[94] compared age-specific fracture rates and BP exposure in various kinds of proximal femur fractures identified by International Classification of Diseases (ICD)– 10 codes. Alendronate exposure was the same in patients with subtrochanteric fractures (ICD-10, S72.2; 6.7%), femoral diaphyseal fractures (S72.3; 7.1%), and the more common femoral neck (S72.0) and intertrochanteric fractures (S72.1; both 6.7%). They

tested the hypothesis that increased risk of subtrochanteric and femoral shaft fractures in patients treated with alendronate exceeded the increased risk of femoral neck and intertrochanteric fractures. Each patient who received alendronate for at least 6 months (n = 5187) was matched with two controls (n = 10,374). In this register-based matched-cohort study, the hazard ratio (HR) for subtrochanteric or diaphyseal fracture with alendronate was 1.46 (95% CI 0.91–2.35, p = .12), similar to the hazard ratio of 1.45 (95% CI 1.21–1.74, p < .001) for femoral neck and intertrochanteric fractures; both estimates were adjusted for comorbidity and concurrent medications. Patients with subtrochanteric and diaphyseal fractures were no more likely to be on alendronate but were more likely to use oral GCs than those with typical hip fractures.

In another national register-based Danish cohort study, 4854 patients without prior hip fracture were followed for a mean of 6.6 years after starting alendronate; data also were obtained from a large matched-cohort analysis of 31,834 alendronate users and 63,668 comorbidity-matched controls over a mean follow-up period of 3.5 years.[95] The overall incidence of subtrochanteric and diaphyseal fractures did not differ between patients in the lowest quartile of cumulative alendronate use (mean 0.2 dose – years) and those in the highest quartile of use (mean 8.7 dose– years), 4.7 per 1000 versus 3.1 per 1000, respectively. In contrast, there was a decline in femoral neck/intertrochanteric hip fracture incidence with increasing dose-years of alendronate from lowest (22.8 of 1000) to highest quartile (10.9 of 1000). The hazard ratio for subtrochanteric/diaphyseal fracture

with alendronate was 1.50 (95% CI 1.31–1.72) compared with 1.29 (95% CI 1.21–1.37) for femoral neck/intertrochanteric hip fracture. Although rates of all fractures were higher in alendronate users than in nonusers, highly compliant patients had significantly lower risk of femoral neck/intertrochanteric fractures (HR = 0.47, 95% CI 0.34–0.65) and subtrochanteric/diaphyseal fractures (HR = 0.28, 95% CI 0.12–0.63).[94] Furthermore, in a small subset of persons who remained highly compliant long term (>6 years), subtrochanteric/ diaphyseal fractures comprised 10% of fractures compared with 12.5% in the control cohort. Consistent with these results, data from another Danish cohort suggest that the risk of subtrochanteric/ diaphyseal fractures and all fractures is present before BP initiation.[96]

In summary, the Danish data indicate no greater risk for a subtrochanteric or diaphyseal femoral fracture in alendronate–treated patients than for an osteoporosis-related fracture of any part of the femur (including the hip).[94,95] Studies of this type provide important broad and contextual data on the epidemiologic characteristics and incidence of subtrochanteric and diaphyseal femoral fractures. However, there is no adjudication of radiographs, and thus they cannot provide specific information on the clinical and radiographic features of the atypical fractures described in case reports and series versus the more typical fractures seen at the same sites.

No cases of subtrochanteric fractures were reported in preclinical studies or placebo-controlled registration trials of oral BPs involving more than 17,000 patients. However, the maximum duration of BP exposure for most subjects in these trials was less than 4 years.

Recently, however, Black and colleagues[97] reported a secondary analysis of three large randomized clinical trials of BPs, two of oral alendronate, the Fracture Intervention Trial (FIT) and its long-term extension (FLEX), and one of zoledronate (HORIZON-PFT). FIT randomized women to alendronate or placebo for 3 to 4.5 years. In FLEX, 1099 women originally randomized to alendronate were rerandomized to alendronate 5 or 10 mg/day or placebo. The total duration of alendronate was 10 years for those randomized to alendronate and 5 years for those randomized to placebo. In the HORIZON trial, 7736 women were randomized to zoledronate 5 mg or placebo and followed for 3 years. All 284 hip and femur fractures were reevaluated to identify femoral shaft fractures and assess features of atypia. However, the reevaluation was based on the radiographic report because radiographs were available for only one subject. Twelve subtrochanteric/diaphyseal fractures (4%) were found in 10 subjects, 3 of whom had not received BPs. The relative hazard ratios of alendronate versus placebo were 1.03 (95% CI 0.06–16.5) in FIT and 1.33 (95% CI 0.12–14.7) in FLEX. The relative hazard ratio of zoledronate versus placebo was 1.5 (95% CI 0.25–9.0). The authors concluded that the risk of subtrochanteric/diaphyseal fracture was not significantly increased, even among women treated for as long as 10 years. Although the FLEX data that compare 5 and 10 years of alendronate treatment provide some reassurance regarding reported associations of subtrochanteric/diaphyseal fracture with long-term BP treatment, this study had a number of very important limitations.[98] Radiographs were

not available to evaluate features of atypia. Only a minority received more than 4 years of BP, and some received a lower dose of alendronate (5 mg) than commonly prescribed. Most important, because of the rarity of these fractures, statistical power was extremely low.

Preliminary data are now available on the incidence of atypical femoral fractures from a large US health maintenance organization (HMO) that serves 2.6 million people over age 45.[99] Using electronic data sources, 15,000 total hip and femur fractures were identified by both ICD-9 and Current Procedural Terminology (CPT) coding in patients older than 45 years over a 3-year period between 2007 and 2009. After excluding fractures above the subtrochanteric region and below the distal femoral flair and periprosthetic, pathologic, and high-trauma fractures, 600 radiographs were reviewed, of which 102 (~17%) had features of atypia (ie, transverse fracture with short oblique extension medially, cortical thickening, periosteal callus on the lateral cortex). Most (97 of 102) patients had taken a BP. Based on the number of patients receiving BPs in the HMO, preliminary estimates of atypical femoral fracture incidence increased progressively from 2 per 100,000 cases per year for 2 years of BP use to 78 per 100,000 cases per year for 8 years of BP use. These data suggest that atypical femoral fractures are rare in both the general population and BP-treated patients, but their incidence may increase with increasing duration of BP exposure. However, there was no age-matched control group of patients who did not use BPs, and it is possible that the incidence of all fractures in women at this age would increase over 6 years. Important

strengths of this study include the expert adjudication of all 600 radiographs of the region of interest and availability of data on filled prescriptions for oral BPs.

Summary of epidemiologic studies. It is important not to equate the anatomic entity of subtrochanteric/diaphyseal femoral fracture with that of atypical femoral fractures. In addition to location, the latter diagnosis should include all other major features outlined in the case definition (Table 1). The interest in subtrochanteric and diaphyseal fractures in an epidemiologic context is that the total number of these fractures marks the upper boundary of any potential harm owing to atypical femoral fractures. Notably, subtrochanteric and diaphyseal fractures together account for only about 5% to 10% of all hip/femoral fractures; of these, only a subset is atypical (17% to 29%). The proportion of subtrochanteric and diaphyseal fractures that have features of atypia depends on whether fractures owing to high-impact trauma or periprosthetic fractures are excluded and varies in the different patient series from 17%(99) to 29%.[100] It is this subset of fractures that has been associated with the use of BPs, an association that may or may not be causal. It is also important to note that atypical fractures have been reported in patients who have not been exposed to BPs. This occurred in 3 of the 8 patients with atypical fragility fractures of the femur reported by Schilcher and colleagues,[101] in 1 of 20 patients in the Neviaser case series,[100] in 5 of 102 patients reported by Dell and colleagues,[99] in 1 of 4 patients reported by Bunning and colleagues,[102] and in 3 of 26 patients in the Lenart study,[93] as well as in patients with hypophosphatasia.[2,103]

Epidemiologic studies show that fractures of the subtrochanteric region of the femur and the femoral shaft follow an age and sex distribution similar to osteoporotic fractures. However, decreases in age-specific hip fracture rates in the community have not been accompanied by decreases in the rates of subtrochanteric or diaphyseal femoral fractures despite similarities in epidemiology and an association with BMD. While register–based studies provide useful information on the prevalence and incidence of subtrochanteric/diaphyseal fractures, it is important to recognize that these studies rely on diagnostic codes for case finding that may misclassify fracture location[104] and do not assess the radiologic hallmarks of atypia. Thus a stable total number of subtrochanteric fractures potentially could mask a shift from typical osteoporotic subtrochanteric fractures toward more atypical fractures, as might be suggested by Dell's results[99] and those reported by Wang and Bhattacharyya.[90]

If BPs are targeted to patients with a fracture risk similar to that in FIT,[105] using alendronate in women without baseline vertebral fractures, about 700 nonvertebral and 1000 clinical vertebral fractures would be avoided per 100,000 person-years on treatment. In women with prior vertebral fractures, the corresponding numbers are 1000 and 2300.[106] Based on the assumption that up to one in three subtrochanteric fractures is atypical, these numbers are 13 and 29 times higher, respectively, than the 78 per 100,000 incidence figure reported by Dell and colleagues[99] and 10 and 23 times higher, respectively, than the highest estimate of the rate of atypical subtrochanteric/ diaphyseal fractures of 100 per

100,000 in long-term users of alendronate from the Danish study.[95] Thus the risk-benefit ratio clearly favors BP treatment in women at high risk of fracture.

Atypical subtrochanteric and femoral shaft fractures: Clinical data

In its review of published case reports and series as described in "Methods," the task force recognized that the quality of the evidence reported in a substantial proportion was poor, with missing important historical or clinical information. The task force recommends that a hierarchy of data quality should be established for all future studies reporting cases of atypical femoral fractures. The data quality for a case would be based on the quality in seven areas, as indicated in Tables 3 and 4.

Case series and case reports. The total number of reported cases was 310 after overlapping case reports had been excluded (Table 5); 286 cases occurred in association with BP treatment for osteoporosis and 5 in patients with BP treatment for malignancy (ie, myeloma or metastatic renal cell carcinoma). In 19 cases, BP use was not identified. The subjects ranged in age from 36 to 92 years. Only nine fractures were in men, but gender was not identified in three large case series.[100,107,108] The majority (160 of 189) occurred after oral alendronate monotherapy: 12 patients were treated with oral risedronate (of these, 1 was followed by oral alendronate, whereas 2 were treated previously with alendronate and another was treated previously with pamidronate), 4 with a combination of intravenous pamidronate followed by intravenous zoledronic acid (myeloma), 4 with either oral or intravenous pamidronate (osteoporosis), 2 with

intravenous zoledronic acid (renal cell carcinoma and osteoporosis), 2 with oral alendronate followed by oral ibandronate, and 102 with an unspecified oral BP.

Table 3. Hierarchy of Data Quality for Atypical Femoral Fractures

The quality of evidence should be assessed for the following key areas:

1. Patient characteristics
   a. Age
   b. Gender
2. Description of atypical subtrochanteric and femoral shaft fracture
   a. Location in femoral shaft from just distal to the lesser trochanter to just proximal to the supracondylar flair of the distal femoral metaphysis
   b. Presence of transverse or short oblique configuration of fracture
   c. Low level of trauma
   d. Noncomminuted
   e. Presence of thickened cortices with or without a periosteal callus
3. Bisphosphonate exposure history
   a. Specific drug(s)
   b. Specific dose history
   c. Duration of and adherence to therapy before diagnosis of fracture
4. Bisphosphonate therapy indication
   a. Disease (osteoporosis, osteopenia, myeloma, etc.)

b. History of prior low-trauma fracture

5. Comorbid conditions
   a. Presence of vitamin D deficiency (<20 ng/mL)
   b. Presence of other comorbid conditions
      - RA
      - Other diseases requiring corticosteroids
      - Diabetes
      - Cancer
      - Hypophosphatasia
6. Concomitant medication history
   a. Identity of concomitant medications, including
      - Glucocorticoids
      - Proton pump inhibitors
      - Other antiresorptive drugs (eg, estrogen, raloxifene, calcitonin, denosumab)
   b. Doses of concomitant medications and duration of therapy prior to subtrochanteric fracture
7. Investigations
   a. Bone densitometry
   b. Bone turnover markers
   c. Bone histomorphometry, including an assessment of bone turnover

The duration of BP therapy ranged from 1.3 to 17 years, although duration was not identified in 1 patient. The median duration was 7 years. The presence or absence of prodromal pain was assessed in 227 of 310 patients; it was present in 70% (158 of 227). Concomitant GC use was assessed in 76 of 310 patients; it was present in 34% (26 of 76) and increased the risk of subtrochanteric fractures in one large series

(OR = 5.2).[107] Bilateral fractures were assessed in 215 of the 310 patients and were present in 28% (60 of 215). Bilateral radiologic changes were assessed in 224 of the 310 patients and were present in 28% (63 of 224). Healing was assessed in 112 of the 310 patients and was reported to be delayed in 26% (29 of 112).[13,102,109–119] In one large series, other historical risk factors associated with subtrochanteric fractures were a prior low-trauma fracture (OR = 3.2), age younger than 65 years (OR = 3.6), and active RA (OR = 16.5). PPI use was assessed in 36 of the 310 patients and was noted in 14 (39%) [112,119–121]

Table 4. Classification of Data Quality

The overall hierarchy of evidence quality for a case would be based on the quality of these seven areas:

Best evidence:

Information complete for all seven categories

Good evidence:

Information complete for categories 1–5, 6a, and 7a

Acceptable evidence:

Information complete for categories 1–4, but 5, 6a, and 7a not all complete

Marginal evidence:

Information complete only for categories 2a and 3a

Insufficient evidence:

Information unavailable for categories 2a, 3a, and 4a regardless of other information provided

Serum 25-hydroxyvitamin D [25(OH)D] concentrations were measured in 84 patients, and 5 (6%) had vitamin D deficiency [25(OH)D < 20 ng/mL]. In one large series, serum 25(OH)D concentrations of less than 16 ng/mL increased the risk of subtrochanteric fractures (OR = 3.2). Of the 67 patients who had bone densitometry recorded, 45 (67%) had osteopenia or normal BMD.

Relatively few reports included bone turnover markers (BTMs).[13,109,113–116,122,123] When measured, however, bone resorption markers are usually within the normal premenopausal range[109,114–116,123,124] and occasionally are elevated.[114,115,122] In only a minority of cases have BTMs been suppressed.[13,109,116] Thus BTMs, at least when measured after atypical femoral fractures have occurred, do not suggest oversuppression of bone turnover in the majority of patients. However, since fractures per se are associated with increased BTMs, measurements obtained after a fracture may reflect fracture healing rather than the rate of bone remodeling throughout the skeleton. BTM determination prior to the fracture would be more informative.

Summary of case series and case reports. Several case series and multiple individual case reports suggest that subtrochanteric and femoral shaft fractures occur in patients who have been treated with long-term BPs. However, these fractures also may occur in BP-naive patients. Several unique radiographic and clinical features have emerged from these case reports and series. All the individual case reports of atypical femoral fractures[118,119,122,125–129] illustrate one or more radiographic features suggestive of a fracture distinct from the common osteoporosis-, prosthesis-, or major

trauma–related fractures. These include lack of precipitating trauma,[118,122,127] bilaterality (either simultaneous or sequential),[118,119,122,129] transverse fractures,[127] cortical hypertrophy or thickness,[118] stress reaction on the affected and/or unaffected side,[118,122,125,127,129] and poor fracture healing.[118,128] Other features include prodromal pain in the thigh or groin for weeks or months prior to the fracture,[118,122,127] use of an additional antiresorptive agent (eg, estrogen, raloxifene, or calcitonin), use of GCs or PPIs in addition to the BP,[118,119,125] presence of RA or DM, serum 25(OH)D concentrations less than 20 ng/mL, and normal or low BMD but not osteoporosis in the hip region.[13,115,119] Several reports describe iliac crest biopsies with very low bone turnover rates (Table 6); however, this is not a distinguishing feature of patients with atypical fractures on BPs because even short-term use of a BP results in dramatic reductions in rates of bone turnover.[119,130] BTMs have not shown any consistent pattern but are often not suppressed. In sharp contrast to prior experience with osteonecrosis of the jaw,[131] the number of cases of atypical fracture reported in cancer patients receiving high-dose intravenous BPs is substantially lower than those in patients being treated for osteoporosis. Whether this is a reporting bias remains to be seen. However, if true, this would argue against a simple causal relationship with the amount of BP received and perhaps suggests that duration may be more important than amount.

Guisti and colleagues conducted a systematic review of 141 women with postmenopausal osteoporosis treated with BPs who sustained

subtrochanteric/diaphsyeal fractures.[11] Their results are generally comparable with this task force report with regard to age, mean duration of BP use, proportions with bilateral fractures, prodromal pain, comorbid conditions (ie, DM or RA), and concomitant use of estrogen, raloxifene, tamoxifen, and GCs. They also reported that patients with subtrochanteric versus femoral shaft fractures had a higher number of comorbid conditions, were more likely to have bilateral fractures, and were more often using PPIs. Patients who had used BPs for less than 5 years were more likely to be Asian and to have had a femoral shaft fracture prior to initiating BP therapy.[11]

It is highly likely that case reports and case series of atypical femur fractures will continue to accumulate. In this regard, abstracts submitted to the 2010 Annual Meeting of the ASBMR[132–136] reported another 47 cases not included in this analysis. Many physicians who treat substantial numbers of patients with osteoporosis have described additional cases anecdotally, the majority of which are unlikely to be published. Similarly, cases may not be reported owing to lack of recognition by clinicians. Thus there is concern that the reported cases represent a minority of the actual number of cases that exist.

Bone histology and histomorphometry. A substantial number of the case studies have included histomorphometric analysis of iliac crest bone biopsies (Table 6). However, only a few reports have included histology or histomorphometry of bone taken from or close to the subtrochanteric fracture site. Iliac crest biopsies generally have revealed extremely low bone turnover, a finding consistent with BP treatment,[137–139] especially in patients treated concomitantly with a

BP and another antiresorptive agent, such as estrogen,[140] or with BPs and GCs.[141] Although a number of reports mention lack of double tetracycline labels in the biopsy, this too is a common and expected finding in BP-treated subjects,[138,139] even in those who have been treated for only 6 months.[130] Moreover, lack of double label or so little double label that mineral apposition rate cannot be evaluated reliably is seen in a significant proportion of untreated postmenopausal women.[142,143] Static parameters of bone formation are also low in biopsies from patients with atypical femoral fractures, consistent with those seen in BP– treated patients with osteoporosis. It is important to note that a finding of low turnover in biopsies from BP-treated patients with atypical femoral fractures has not been universal.[109,119] In most cases, only a single transiliac biopsy, usually taken soon after the fracture, has been studied. Therefore, the turnover status prior to the fracture or before beginning BPs is not known. However, in one report,[126] a 35-year-old man was biopsied before beginning alendronate and again 7 years later, after a low-trauma subtrochanteric femur fracture. The first biopsy revealed low trabecular bone volume, reduced trabecular connectivity, and increased osteoid surface and tetracycline uptake, consistent with high-turnover osteoporosis. In contrast, the postfracture biopsy showed lack of osteoid and tetracycline labels, confirming conversion of high– to low-turnover bone.

Table 5. Case Series and Reports of Atypical Fractures

[see next page for table]

Author/date/reference	Number of patients	Age (range)	Gender (M/F)	BP exposure	BP duration (years)	Bilateral fractures/ radiographic changes (n)	Prodrome (n)	Oral GCs (n)	Serum 25 (OH)D < 20 ng/mL (n/available)	Hip T-score >−2.5 (n/available)
Goh, 2007[116]	9	55–71	0M/9F	9 ALN	2.5–5	1/3 (thick cortex)	5	1	NA	5/5
Kwek, 2008[117]	17[a]	55–77	0M/17F	16 ALN, 1 ALN > RIS	2–10	4/5	13	1	NA	8/12
Neviaser, 2008[180]	19[b]	NA	NA	19 ALN	Mean 6.9 (in 10 patients)	NA/NA	NA	NA	NA	NA
Wernecke, 2008[119]	1[c]	72	0M/1F	ZA > PAM	11	1/0	1	0	NA	1
Odvina, 2005[114]	5	52–68	1M/4F	5 ALN	5–8	2/NA	NA	2	None	5/5
Odvina, 2010[118]	11	38–77	0M/11F	9 ALN 2 RIS	2–11	5/NA	5	4	2/9 (range: 28–180) (range: 17.0–33.0)	5/8
Visekruna, 2008[181]	3	51–75	0M/3F	3 ALN	5–10	2/NA	2	3	None (range: 32–48)	3
Somford, 2008[115a]	1	76	0M/1F	ALN	8	1/0	1	1	1 (16.8)	1
Demiralp, 2007[115b]	1	65	0M/1F	ALN	7	1/0	1	1	NA	0
Armamento-Villareal, 2009[120]	7	43–75	1M/6F	6 ALN 1 RIS	2–10	2/NA	NA	0	(30.6)	4/5
Lee, 2007[115c]	1	73	0M/1F	ALN	1.6	0/1 (thick lateral cortex)	1	0	None (24)	1
Schilcher, 2009[102]	5	>75	0M/5F	NA	3.5–8.5 (mean 5.8)	1/NA	NA	NA	NA	NA
Ing Lorenzini, 2009[115]	8	57–86	1M/7F	5 ALN 1 RIS > ALN 1 ALN > IBN 1 PAM	1.3–10.3	4/3 (thick lateral cortex)	2	3	NA	3/4
Schneider, 2006[110]	1	59	0M/1F	ALN	7	0/0	1	NA	NA	1
Seyed Noor, 2008[111]	1	72	0M/1F	ALN	7	0/1 (thick cortex with local lateral cortical reaction)	1	NA	NA	NA
Seyed Noor, 2009[175]	2	55–78	0M/2F	2 ALN	9	0/1 (cortical hypertrophy with lateral cortical reaction)	2	0	NA	NA
Goddard, 2009[121]	1	67	0M/1F	ALN > IBN	17	1/0	0	0	NA	NA
Cheung, 2007[122]	1	82	0M/1F	ALN	10	1/0	0	0	"Normal"	1
Bush, 2008[115d]	1	61	1M/0F	ZA	1.5	0/1 (thick diaphyseal cortex)	0	0	NA	NA
Capoci, 2009[182]	7	53–75	0M/7F	7 ALN	5–13	3/4 (cortical stress reaction)	4	NA	0/3 (21–39)	NA

Author/date/reference	Number of patients	Age (range)	Gender (M/F)	BP exposure	BP duration (years)	Bilateral fractures/ radiographic changes (n)	Prodrome (n)	Oral GCs (n)	Serum 25 (OH)D < 20 ng/mL (n/available)	Hip T score >−2.5 (n/available)
Husada, 2005[illegible]	1	72	0M/1F	ALN	NA	1/0	1	NA	NA	NA
Edwards, 2010[illegible]	1	60	0M/1F	ALN	6	1/1	1	1	NA	1
Cermak, 2009[illegible]	3	59–70	0M/3F	ALN	5.5–12	1/1	2	0	NA	NA
Ali, 2009[illegible]	1	82	0M/1F	ALN	8	0/0	0	0	"Normal"	1
Koh, 2010[illegible]	32[a]	47–91	0M/32F	30 ALN 1 ALN > RIS 1 ZA	2–10	NA/NA	NA	NA	8/32 (median 26.7 μg/L)	NA
Grasko, 2009[illegible]	1	57	1M/0F	PAM > ZA	9	0/0	1	1	NA	1
Napoli, 2010[illegible]	1	56	0M/1F	PAM > ZA	6	0/0	1	1	0	1
Issacs, 2010[illegible]	40	NA	NA	40 ALN	7.1 (mean)	NA/18	29	NA	NA	NA
Girgis, 2010[illegible]	20	78	NA	15 ALN 2 RIS	5.1 ALN (mean) 3.0 RIS (mean)	NA/NA	NA	OR 5.2	OR 3.5	NA
Glennon, 2009[illegible]	6	60–87	0M/6F	5 ALN 1 RIS	1.5–10 ALN 3.0 RIS	0/1 (cortical hypertrophy with lateral cortical reaction)	5	NA	"Normal"	NA
Bunning, 2010[illegible]	4	49–59	1M/3F	1 PAM > ZA 2 ALN 1 No BP	5–5.5	1/1 1 (cortical hypertrophy with lateral cortical reaction)	4	NA	NA	3
Lee, 2009[illegible]	1	82	0M/1F	ALN	8	1/1	NA	NA	None	1
Lering, 2009[illegible]	6	73–81	0M/6F	ALN	0.5–6	0/0	1	0	2	2
Schneider, 2009[illegible]	3	99–66	0M/3F	ALN	5–9	0/2 (cortical hypertrophy with lateral cortical reaction)	2	NA	NA	NA
Somford, 2009[illegible]	3	65–79	0M/3F	ALN	4–12	1/1	3	3	0	1
Giusti, 2010[illegible]	8	36–75	0M/8F	ALN (3) PAM (2) PAM > RIS (1) RIS (2)	2.5–8 ALN 5–6 RIS 3–7 PAM	2/2 3 (cortical hypertrophy with lateral cortical reaction)	5	5	0	3
Dell, 2010[illegible]	102	45–92	3M/99F	Oral BPs (97) No BPs (5)	5.5	26 (complete fracture or stress fracture)	71	NA	NA	NA

NA — data not available; n — number; None — no cases outside the range; RP — oleonosomonate; ALN — alendronate; RIS — risedronate; IBN — ibandronate; ZA — zoledronate; PAM — pamidronate; GC — glucoglucocorticoid; OR — odds ratio.

[a]This report included 8 from Gen, with substantial overlap likely[illegible].

[b]This report included 10 from Lenart[illegible].

[c]Unclear whether included in Neviaser[illegible].

[d]This report included 17 from Kwes[illegible].

Table 6. Histomorphometric and Pathologic Assessments.

Author/date /reference	Number of patients biopsied	Site	Parameters	Findings
Goh, 2007	5	Fracture site	Qualitative	No malignancy
Bush, 2008 (a)	1	Fracture site	Qualitative	No malignancy; no osteoclasts
Wemecke, 2008 (a)	1	L Femoral head, neck, marrow R Fracture site	Qualitative	L: No myeloma R: Thin, sclerotic trabeculae Absent osteoclast/osteoblast activity
Somford, 2009	2	Fracture site	Qualitative	No malignancy; no "osteoporosis"
Ing-Lorenzini, 2009	2	Fracture site	Qualitative	Absent fracture healing/remodeling in cortex ½; periosteal bridging
Aspenberg, 2010	1	Fracture site	Qualitative	Few osteocytes distant from fracture; increased Oc.N and Ot.N near fracture; loss of osteonal regular structure indicating enhanced remodeling

Samford, 2009	1	Fracture site and iliac crest	Static	Increased resorption and reduced formation at both sides; Oc.N sixfold higher at femoral cortex than iliac crest
Lee, 2009	1	Fracture site	Static	Absence of osteoclasts and osteoblasts; few osteocytes; hypercellular marrow No inflammation or malignancy; irregular/disorganized collagen matrix
Donnelly, 2010	14(c)	Fracture site	Static, Material Properties	Normal architecture and OS; reduced heterogeneity
Odvina, 2005	9	Iliac crest	Static and Dynamic	Reduced bone turnover in all; no double labels 9/9; single labels 5/9
Cheung, 2007	1	Iliac crest	Static and Dynamic	Reduced osteoblast/osteoclast activity; thin but extensive osteoid
Visekruna, 2008	2	Iliac crest	Static and Dynamic	Case 1: Increased Oc.N; lower OS and O.Wi; no double labels; limited single labels Case 3: increased Oc.N and Ob.N; lower OS and O.Wi; double and single labels; low activation frequency
Armamento -Villareal, 2009	7(b)	Iliac crest	Static and Dynamic	Reduced bone turnover 5/7; normal turnover 2/7
Odvina, 2010	6	Iliac crest	Static and Dynamic	Ob.S and OS absent or low 6/6; Oc.S absent or low 3/6; ES normal 5/5; double labels absent 4/6; single labels present 4/6

Giusti, 2010	1	Iliac crest	Static and Dynamic	Decreased Oc.N, ES, and OS; reduced turnover; few labels
Armamento-Villareal, 2006	1	Iliac crest	Qualitative	Pre-ALN: increased OS and labels; post-ALN: 6 years, no osteoid or labels
Leung, 2009	1	Iliac crest	Qualitative	Decreased Oc.N and Ob.N; reduced bone turnover; no labels
Napoli, 2010	1	Iliac crest		Unsuccessful; bone too "hard"

Oc.N = osteoclast number; Ob.N = osteoblast number; OS = osteoid surface; O.Wi = osteoid width; Oc.S = osteoclast surface; Ob.S = osteoblast surface.

(a) Cancer patients treated with high-dose BPs, i.v.

(b) Biopsies performed on 15 patients, but only 7 had femoral shaft fractures.

(c) All BP treated, average duration 7.4 years; 4 atypical femoral fractures, 1 subtrochanteric, 9 intertrochanteric

In several cases, biopsy samples were obtained at or close to the site of the subtrochanteric fracture, the location that is likely to provide more information on the underlying pathogenetic mechanism, although there is no opportunity for tetracycline labeling and dynamic assessment of bone turnover in this setting. Moreover, analysis at the biopsy site may be misleading because the fracture itself will lead to an acceleration of remodeling in the region of the fracture. Caution should be used in interpreting measurements of bone turnover taken from a biopsy at the fracture site. Ing-Lorenzini and colleagues[112] obtained biopsies from two patients but described the histologic appearance of only one of those, a 65-year-old postmenopausal woman who had received alendronate for 5 years and ibandronate for 1 year before suffering a subtrochanteric right femoral shaft insufficiency fracture. Five years earlier and 2 years after starting alendronate, she had sustained a subtrochanteric fracture of her left femur. This patient also had been treated with tibolone, inhaled GCs, and a PPI. A biopsy taken from the lateral cortex exactly at the level of the second fracture showed a fracture line extending from the periosteal to the endosteal surface with evidence of partial bone bridging across the fracture line on the periosteal surface. The fracture line was filled with blood, and there was no evidence of intracortical remodeling.

Lee[113] obtained a biopsy of endocortical bone from the proximal end of the fracture in an 82-year-old woman who had sustained bilateral atypical femoral fractures. She had been treated with alendronate for 8 years. Osteoclasts were not seen in the sample, and osteocytes were few in number. Polarized light

revealed the presence of both lamellar and woven bone. The bone marrow was hypercellular, but there was no evidence of inflammation, malignancy, or myelosclerosis. Goh and colleagues[10] performed qualitative histology on biopsies removed intraoperatively during repair of subtrochanteric fractures in 5 alendronate-treated patients, but they simply reported that there was no evidence of neoplasia.

Napoli and colleagues [144] described one of the few reported cases of atypical femoral fracture in a cancer patient (multiple myeloma) treated with high-dose intravenous BPs. Following a stem cell transplant, the patient was given pamidronate for 2 years and zoledronate for 4 years, in addition to high-dose GCs. An attempt to obtain an iliac crest biopsy was unsuccessful because the biopsy needle was unable to penetrate the "rock hard" bone. Wernecke and colleagues[123] reported another case of a patient with multiple myeloma who had been treated with intravenous BPs (pamidronate and zoledronate) for 9 years and presented with sequential, bilateral subtrochanteric stress fractures. Histologic examination of a biopsy taken from the femoral head during repair of the second fracture revealed an almost complete lack of osteoclasts and osteoblasts. A similar finding was described in curettage samples from the fracture site of a patient who had been treated with intravenous zoledronate for 1.5 years to prevent metastatic bone disease secondary to renal carcinoma.[145]

In contrast to the preceding cases, the biopsy from the subtrochanteric fracture site obtained by Somford and colleagues[119] revealed a very different cellular

profile. This biopsy was taken from a 76-year-old woman with RA who had been treated with alendronate for 8 years prior to admission for a subtrochanteric stress fracture of her left femur, which subsequently fractured completely. She also had received GCs and methotrexate for 11 years and infliximab for 3 years before the fracture. Nine months after the left femur fracture, she sustained a subtrochanteric fracture of her right femur. At that time, biopsies were obtained from the iliac crest and the right femur approximately 1 cm above the fracture. In the ilium, cancellous bone microarchitecture was normal for her age, but static bone formation indices, such as osteoid surface and volume, were reduced substantially to within the range previously reported for patients with alendronate-treated, GC– induced osteoporosis.[141] Unexpectedly, the eroded surface was about threefold higher than that of controls and 6.5 to 13 times the levels seen in patients with GC-induced osteoporosis and postmenopausal osteoporosis, respectively. Osteoclast number also was about four times higher than that recorded in alendronate-treated patients; however, this is not surprising because normal or elevated numbers of osteoclasts have been reported from biopsies of BP-treated patients.[146] In a biopsy taken close to the fracture site, eroded surface and osteoclast number were high, and static parameters of bone formation were low, although there are no normative data for this skeletal site. Osteoclast number at the fracture site was sixfold higher than at the iliac crest. At both sites, the morphologic appearance of the osteoclasts suggested that they were actively resorbing. The imbalance between resorption

and formation displayed by this patient differs from the prevailing hypothesis regarding the pathogenesis of atypical fractures, which invokes severe suppression of turnover. It is possible that the excessive resorption was related to the fracture itself, but this seems unlikely, given that it also was evident in the iliac crest biopsy and that the femoral biopsy was located 1 cm above the fracture and was taken within 12 hours of the event. MRI evidence for excessive resorption at the site of atypical fractures also has been reported in a BP-treated patient,[12] and the same phenomenon injuries.[147,148] Somford and colleagues[11] also took the opportunity to assess the mineralization density of the bone tissue at the fracture site because some have suggested that prolonged BP treatment may lead to hyperm neralized and, therefore, brittle bone matrix. There was no evidence of hypermineralization and no change in hydroxyapatite crystal size, although the crystals were more mature than in control subjects, consistent with the known effects of alendronate on bone turnover and secondary mineralization.[119]

Summarizing the small amount of histologic data currently available in patients with atypical fractures, most, but not all, studies indicate very low turnover at both the iliac crest and the fracture site, although reports of increased turnover may be influenced by the fracture itself. Also, only static and qualitative histomorphometry analyses at the fracture site are available. Whether turnover at the iliac crest is lower than in the vast majority of BP-treated patients who have not sustained such fractures is not known. Double tetracycline labels are usually absent, but single labels are present in many cases, indicating

that turnover is not always absent at the ilium. Also, where available, biochemical markers of bone turnover are often not reduced to the same degree as that seen in the biopsy and may be within the normal range.[13,109,113–116,122,123] The findings of Somford and colleagues[119] at both the ilium and the fracture site and of Visekruna and colleagues[12] at the ilium suggest an alternate pathogenetic mechanism that involves increased resorption coupled with reduced bone formation. Clearly, more information is needed about bone histopathology at the site of atypical femur fractures (see "Key Research Questions" below).

Input from the pharmaceutical industry. Four members of the task force (DB, TB, RM, and ES) conducted teleconference sessions with representatives of companies that market drugs used to treat osteoporosis in the United States (ie, Amgen, Eli Lilly, Genentech, Merck, Novartis, and Warner-Chilcott). These sessions were informational; they permitted the task force to develop some understanding of the number of atypical fracture cases reported to the industry and the steps being taken by the individual companies to adjudicate cases reported to them. The sessions also permitted experts from the industry to provide their input on the case definition for consideration by the task force.

Most of the companies had examined the data from their large registration trials, and very few cases of atypical femoral fractures were detected. However, this approach was limited in most cases by reliance on diagnostic codes to search for subtrochanteric and diaphyseal fractures and lack of availability of radiographs to examine features of atypia in any subtrochanteric/diaphyseal fractures that occurred.

Also, maximum treatment duration in these trials was lower than the median treatment duration in the published cases of atypical fractures. Most cases were from the postmarketing reporting system. These are unsolicited reports of medical events temporally associated with use of a pharmaceutical product and originating from health care professionals, patients, regulatory agencies, the scientific literature, and the lay press. Although this system is useful for identifying rare events that are not detected in clinical trials, important limitations include underreporting and poor-quality reports with missing critical information. Additionally, it is impossible to calculate incidence rates; the numerator is uncertain because of under–reporting, and the denominator generally is based on the amount of drug distributed. There was considerable variability among companies in the mechanisms in place to identify atypical femoral fractures and in the amount of information that was shared with the task force. The number of patient-years of exposure to drugs that are currently on the market for osteoporosis varied between 2 million and 54 million. In general, reporting rates of subtrochanteric and diaphyseal fractures, with or without atypical features, were very low (1 to 3 per 1 million patient-years of exposure). However, as expected, the pharmaceutical companies were aware of cases that had not been reported in the medical literature.

Input from the USFDA. Two task force members (DB and ES) conducted a teleconference with representatives of the FDA. Data from the FDA were consistent with industry and task force estimates of the number of atypical femoral fractures. However,

officials emphasized that adverse-event reporting was subject to the same limitations noted earlier, particularly substantial underreporting.

Recommend the development of noninvasive diagnostic and imaging techniques with which to better characterize and diagnose the disorder

Imaging of the atypical femoral shaft fracture is relatively straightforward. Conventional radiography is the first line of approach, with more sophisticated imaging such as bone scintigraphy, magnetic resonance imaging (MRI), or computed tomography (CT) useful principally for detecting early or subtle prefracture features.[12,93,100,119,145]

Conventional radiographs of the femur, acquired in anteroposterior and lateral projections, usually suffice to demonstrate a range of characteristic findings in complete or incomplete fractures[149–152] (Fig. 2*A*). These consist of a substantially transverse fracture line, at least laterally, with variable obliquity extending medially (Fig. 3). There is often associated focal or diffuse cortical thickening, especially of the lateral cortex, where the fracture process generally initiates. When it is focal and substantial, this lateral cortical thickening may produce an appearance of cortical "beaking" or "flaring" adjacent to a discrete transverse fracture line[12,93,100,145] (Fig. 2*B*). As the fracture evolves and propagates medially, ultimately displacing and becoming a complete fracture, an oblique component may be observed as a prominent medial "spike" (Fig. 2*A*). Conventional radiography also may show diffuse cortical thickening, suggesting chronic stress response, which may be unilateral or bilateral (Fig. 3). Similarly, discrete linear lateral

cortical translucencies may be observed in the pre–fracture displacement phase, often with adjacent focal cortical thickening from periosteal new bone apposition[12,93,100,145] In contrast, femoral stress fractures of athletes usually involve the medial cortex in the proximal one-third of the diaphysis.[149–152]

While conventional radiographs may be suggestive or diagnostic of these stress or insufficiency fractures even in moderately early evolution, the findings may be quite subtle and nondiagnostic[149,150] (Figs. 4*A*, *C*, and 5*A*). In the setting of prodromal symptoms of aching deep thigh or groin pain and normal or equivocal radiographs, additional, more advanced diagnostic imaging procedures may be useful. Radionuclide bone scintigraphy may be employed to document the presence of an evolving stress or insufficiency fracture.[119,145,149–153] Typically, the appearance will be that of unilateral or bilateral increased uptake with a broad diffuse zone and a centrally located, focal region of extreme uptake usually in the lateral cortex (Figs. 4*B* and 5*B*). When only the diffuse pattern is observed, the differential diagnosis includes primary or secondary malignancy, bone infarction, and osteomyelitis. However, these conditions usually are centered in the medullary space of the femur and do not show the lateral cortical predilection of stress fractures.

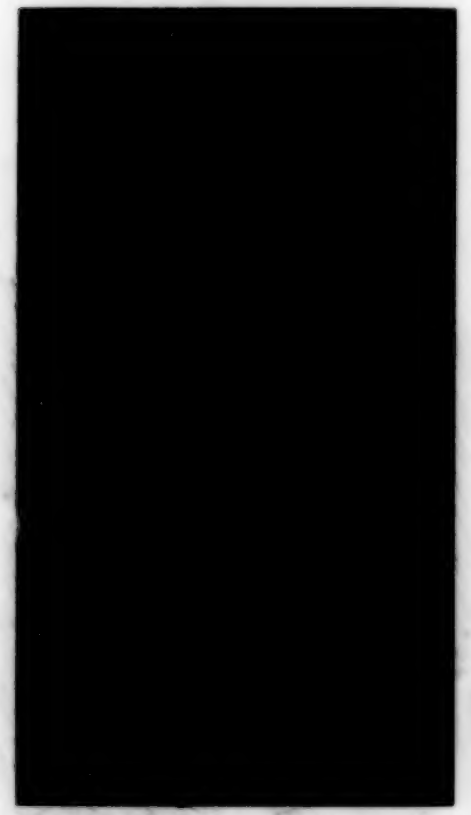

Fig. 3. AP radiograph of the left femur demonstrates a substantially transverse femoral fracture and associated diffuse periosteal new bone formation (*black arrow*) and focal cortical thickening (*white arrow*) consistent with atypical femoral shaft fracture. (*Courtesy of Joseph Lane, MD.*)

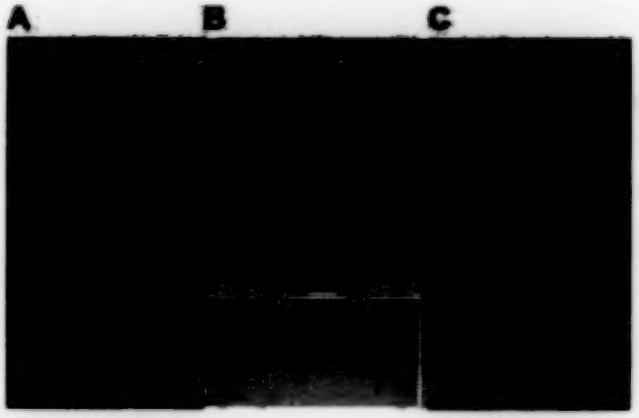

Fig. 4. Conventional AP radiographs of the right (*A*) and left femurs (*C*) demonstrate subtle focal cortical thickening on both periosteal and endosteal surfaces, as well callus on the periosteal surface (*arrows*), whereas bone scintigraphy (B) demonstrates focal increased radionuclide uptake in the corresponding proximal lateral femoral cortices, findings consistent with early, evolving, bilateral femoral insufficiency fractures. (*Courtesy of Piet Geusens, MD.*)

Like bone scintigraphy, MRI can detect the reactive hyperemia and periosteal new bone formation of an evolving stress or insufficiency fracture[151–155] (Fig. 5*C*). Typically, on T1-weighted images there will be diffuse decreased signal owing to both water partially replacing the normal fatty marrow components and the focal cortical thickening that creates little signal on this sequence. On T2-weighted images with fat saturation, there may be diffuse increased signal related to the associated inflammation and hyperemia. With relatively high resolution and multiplanar imaging, the evolving fracture line in the lateral cortex may be discerned on T2-weighted

images or on T1– weighted images obtained with fat saturation and gadolinium–based contrast enhancement. The ability to image thin sections in multiple planes creates both high sensitivity and high specificity, generally surpassing that of bone scintigraphy.

Similarly, the application of advanced multislice or spiral CT imaging with its thin sections, relatively high resolution, and multiplanar re-formation capability renders this technique quite useful in detecting subtle reactive periosteal new bone formation and the small, discrete radiolucency of the evolving fracture and its focal intracortical bone resorption.[156–158]

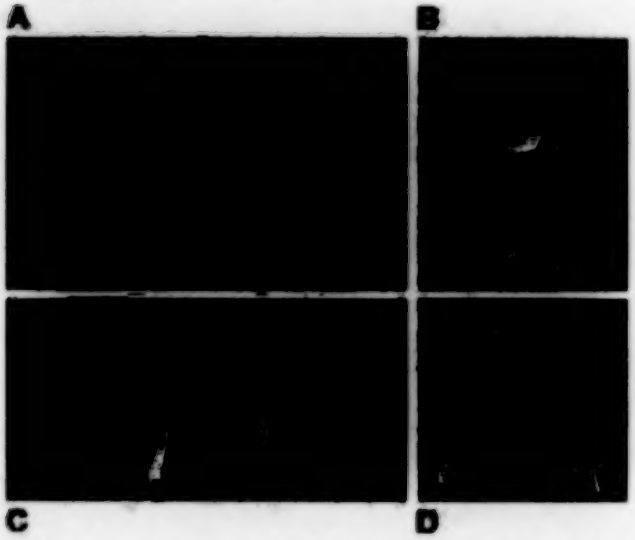

Fig. 5. Conventional AP radiograph of the pelvis (*A*) shows bilateral focal cortical thickening from periosteal new bone formation (*arrows*). Corresponding bone scintigraphy (*B*) demonstrates focal increased radionuclide uptake in the proximal

lateral femoral cortices (*arrows*). MRI images of the femurs (*C*) demonstrate subtle decreased signal on T1-weighted and increased signal on T2-weighted images only of the right femur on this section. Similar findings on AP DXA hip images (*D*) show focal bilateral cortical thickening consistent with early, evolving femoral insufficiency fractures. (*Courtesy of Fergus McKiernan, MD.*)

While scintigraphy, MRI, and CT scanning are more costly and less convenient than conventional radiography, these advanced imaging techniques provide superior sensitivity and specificity for detecting early stages of stress or insufficiency fractures and therefore, in selected instances, could improve the clinical management of atypical femoral shaft fractures (Fig. 5*A–C*). Even the lower-resolution images of dual-energy X-ray absorptiometry (DXA) occasionally may detect the hypertrophic new bone formation of an evolving proximal subtrochanteric femoral shaft fracture and aid in the differentiation of proximal thigh pain in this condition[104] (Fig. 5*D*).

Identify the key questions that the scientific community should address, and recommend a research agenda to elucidate incidence, pathophysiology, and etiology of atypical femoral fractures and their potential relationship with BP usage

Recommendations to facilitate future research

Create specific diagnostic and procedural codes for cases of atypical femoral fractures. To facilitate case ascertainment in administrative data sets and identification of incident cases, specific diagnostic and

procedural codes (ICD and/or CPT code) should be created for atypical femoral fractures based on the major features summarized in the case definition, as has been done recently for osteonecrosis of the jaw (ONJ, ICD-9 733.45). Such codes would facilitate preliminary case ascertainment in administrative data sets, which then would result in more efficient and targeted review of medical records and radiographic images. Having a specific code would permit better understanding of the relative incidence of these fractures compared with other osteoporotic fractures of the lower extremity that otherwise could be coded similarly. Without such a code, it will be more difficult to identify and confirm atypical fractures efficiently in future large population databases where the population at risk can be enumerated. Better precision in determining incidence rates of atypical fractures in large populations will permit examination of health economics and harm/benefit modeling.

Develop an international registry for cases of atypical femoral fractures. Because of the generally low incidence of these fractures, a centralized repository of standardized information will be required to generate the kinds of data and sufficient numbers of cases to understand the incidence, risk factors, and pathophysiology of atypical femoral fractures. The task force strongly recommends the establishment of an international registry spanning interested countries and health care plans with different patterns of BP usage. Local and national databases should be established to maximize case ascertainment. Data sources that contribute to the registry will be most informative if they can enumerate the population at risk (ie, a denominator).

The registry must use a uniform case definition of atypical fractures. All future studies using patients treated or untreated for osteoporosis should collect radiographs of all femoral fractures. Some formal means should be established to collect all radiographs in an electronic repository to allow for review of the variability in fracture pattern. There should be independent review of the radiographic studies to distinguish classic comminuted spiral fractures from noncomminuted transverse or short oblique atypical fractures of the femoral subtrochanteric and diaphyseal regions. Administrative data may be useful to assist in identifying possible cases, and an ideal scenario would link administrative data to medical and pharmacy records and radiographic images (not simply radiographic reports). Certain information on risk factors for fracture should be available from both administrative and clinical data sources (Table 7). An external agency also could follow up and validate FDA adverse– drug-report data in detail both to confirm all reported cases and to accumulate further accurate information on the epidemiology of this rare but important condition. This was considered to be a good model for national regulatory agencies to consider.

The registry should develop a focused standardized case report form to be completed for each case. A balance must be achieved in the recording of vital information because requiring too much information will make it time consuming to report cases and mean that fewer cases will be reported. Ideally, a case report should include information on demographics, fractures, BP exposure (if any), comorbid diseases, and concomitant medications, as summarized in Table 7.

Key research questions

Define measurable characteristics that are associated with atypical femoral fractures. To develop a clinical profile and to determine which patients are susceptible, it is important to define quantitatively features that are considered part of the etiopathology of atypical femoral fractures. For example, case reports and series suggest that cortical thickening at the fracture site is one feature of atypia. However, because cortical thickness varies throughout the diaphysis and also by age, gender, and possibly race, studies that evaluate this characteristic must specify the specific regions for analysis and measurement. A normal range by age, gender, and diaphyseal location should be developed as a first step toward identifying the significance of cortical thickening in the pathogenesis of atypical fractures. It also would be important to determine prospectively the frequency of other characteristics reported in conjunction with atypical femoral fractures, such as

- The frequency of periosteal reaction (ie, callus) associated with a fracture, including the incidence of such reactions in the contralateral nonfractured femur
- The incidence and duration of prodromal thigh pain
- The frequency of bilateral fractures and symptoms

Table 7. Information That Should Be Included in Future Reports of Atypical Femoral Fractures

- Standard demographic data (age, gender, height, weight, race, ethnicity)
- Anatomic location of the fracture (subtrochanteric or diaphyseal)
- Key radiographic features of atypia (see Table 1)
- Information on osteoporosis therapies
  - Doses, routes, duration of, and adherence to osteoporosis therapy
  - Indication for therapy (eg, osteoporosis, osteopenia, bone loss prevention, cancer, Paget disease)
- Prior fracture history
- Concomitant medications: GCs, thiazolidenediones, PPIs, anticonvulsants, statins, HRT, SERMs
- Comorbid medical conditions: Diabetes, RA, chronic kidney disease, malabsorption, errors of phosphate metabolism, joint replacement
- Family history (for genetic studies)
- Bone mineral density: before treatment and at time of fracture
- Biochemistries
  - Serum calcium, creatinine, 25(OH)D, PTH
  - Biochemical markers of bone turnover (P1NP, osteocalcin, total or bone alkaline phosphatase, C-telopeptide)

- Surgical management of the fracture (intramedullary rod, locking plates): documentation of delayed healing

Identify the true incidence of atypical femoral fractures and their association with BPs and/or other conditions characterized by low bone turnover. The precise incidence of atypical femoral fractures is unknown. To clarify the pathogenesis and causality, it is necessary to understand the true incidence of these fractures in the general population of patients without known osteoporosis who are unexposed to BPs, in patients with osteoporosis both exposed and unexposed to BPs and other agents used to treat osteoporosis, and in specific populations distinguished by concomitant drug exposures and comorbid diseases. Without these data, it is possible to misinterpret an association between treatment and fractures as causation. Patients with Paget disease receiving intermittent courses of BPs and patients with malignancies receiving high doses of intravenous BPs also should be assessed, with appropriate controls for duration of treatment, BMD, and other relevant parameters. To determine whether atypical femoral fractures are a class effect of BPs or generally related to low bone turnover, it is essential to determine whether such fractures occur with other antiresorptive drugs, such as estrogen, raloxifene, and denosumab, or in diseases characterized by extremely low bone turnover, such as osteopetrosis, hypoparathyroidism, myxedema, and certain forms of renal bone disease. It also will be important to determine whether the risk of atypical femoral fractures increases with greater inhibition of remodeling. The association between atypical femoral

fractures and concomitant GC therapy is a concern and requires investigation. BPs represent the cornerstone of strategies for the prevention and treatment of bone loss and fractures associated with GCs. However, there are no studies of long-term (>2 to 3 years) BP treatment in patients receiving GCs. Thus, while short-term (1 to 2 years) BP administration lowers the risk of typical osteoporotic fractures in patients with glucocorticoid-induced osteoporosis (GIOP), it is possible that prolonged administration of two classes of drugs that suppress bone formation may increase the risk of atypical femoral fractures.

Acquisition of biopsy data, especially from the site of fracture. Bone biopsy data should be collected whenever possible. Both specimens from the fracture site and tetracycline double-labeled transiliac bone biopsies would be desirable, although the former may be misleading as an indicator of the bone-remodeling rate prior to the fracture. Guidelines for the biopsy size and quality control should be developed. A concerted effort should be made to gather normative data for all these variables from the subtrochanteric femoral shaft. Carefully selected autopsy material would serve for all but the dynamic indices of bone formation. In addition, however, it might be helpful to assess local BMD using microradiographs, micro–computed tomography (mCT), or quantitative backscattered electron microscopy to provide some assessment of collagen organization and to evaluate necrotic bone by measurements of osteocyte apoptosis and/or lacunar density. The information that ideally should be collected from biopsy specimens is summarized in Table 8. Measurement of mechanical

properties, especially tissue properties, would be desirable. It is also important to know whether microcracks accumulate at the site of the femoral fracture and whether there is evidence of healing at the site.

Genetics. Although patients with X-linked hypophosphatemia (XLH) can have pseudofractures that resemble atypical femoral fractures,[2] XLH is usually obvious and only rarely could explain this problem. However, because atypical femoral fractures may resemble the pseudofractures that characterize adult hypophosphatasia,[2] studies to examine the gene that encodes the tissue nonspecific (bone) isoenzyme of alkaline phosphatase (TNSALP) for mutations or polymorphisms will be of research interest for atypical femoral fracture patients. This could clarify whether carriers for hypophosphatasia develop atypical femoral fractures from antiresorptive agents. Genome-wide association studies probably will not be helpful because DNA samples from many atypical femoral fracture patients would be necessary.

Table 8. Information to Be Collected from Transiliac and/or Femoral Fracture Biopsies

- Cortical and cancellous microarchitecture: Bone volume (BV/TV), trabecular thickness (Tb.Th), separation (Tb.Sp) and number (Tb.N); cortical area (Ct.Ar), thickness (Ct.Th), and porosity (Ct.Po)
- Mineral and matrix quality, including mineral density distribution, heterogeneity of matrix characteristics, and mineral particle size and shape

- Collagen cross-links and advanced glycation end products
- Collagen organization (lamellar/woven)
- Osteoblast and osteoclast surface
- Osteoblast and osteoclast numbers, with surface referent
- Prevalence of osteoblast and osteocyte apoptosis per total number of cells
- Amount of necrotic bone, as determined by measurements of lacunar density and empty lacunae
- Osteoid surface, volume, and average thickness
- Reversal surface, with bone surface referent
- Bone-formation rates and activation frequency, when possible
- Bone vascularity
- Tissue mechanical properties

Bone turnover markers. Retrospective analysis of BTM data from fracture patients but prior to the introduction of BP therapy and before the fracture should be performed where possible. Although specific BTMs may not be available, serum total alkaline phosphatase is a commonly performed test and may be useful in assessing whether bone turnover was low before or became suppressed during therapy in these individuals.

The development of an animal model to study pathogenesis. It is unlikely that pathogenesis and fracture mechanism can be fully understood from clinical data alone given the low incidence of these

fractures and the variability in patient characteristics. Once the risk factors contributing to atypical femoral fractures are better understood, animal models incorporating risk factors may provide insights into mechanisms at the cellular and tissue levels. Because bone remodeling is likely an important component of the response, in vivo animal models that exhibit intracortical remodeling are particularly critical. Several different animal models have been used to study the pathogenesis of stress fractures. Existing rodent models[3,4,66] may not be appropriate because of their lack of haversian remodeling, but attempts should be made to adapt fatigue–loading techniques that have been developed in rodents to larger animals. Nonhuman primates would be acceptable but are expensive. Several smaller animal models, such as rabbits and dogs, that have substantial intracortical bone remodeling may be appropriate. However, these animals cannot be studied in conjunction with the osteoporotic condition because attempts to make them estrogen-deficient generally do not result in bone loss. Sheep have some intracortical remodeling and can be made estrogen-deficient. However, they have some reproductive anomalies and are seasonal breeders, which may limit their usefulness. Minipigs might offer a suitable alternative, although adult minipigs can be difficult to handle and are expensive.

Because of the similarity of the signs and symptoms preceding atypical femoral fractures to stress fractures, it may be desirable to combine variable loading regimens (eg, increased mechanical loading or fatigue injury) with a concurrent pharmacologic regimen that could accelerate the development of bone fragility. Animals do not appear to fracture

spontaneously, even following prolonged treatment with high doses of second– and third– generation BPs. For this reason, the endpoints of such studies should not be overt fracture. Rather, animal models can be used to investigate alterations in the structural and material properties of the bone under different conditions, such as coadministration of GCs and BPs or administration of BPs to diabetic animals. They also could be used to explore possible regional differences in the biodistribution of various BPs, bone histomorphometry and microarchitecture, bone healing, and bone vascularity. Efforts at management of stress-induced lesions (eg, treatment with parathyroid hormone) also should be examined in such models.

Recommend clinical orthopedic and medical management of atypical femoral fractures based on available information

Surgical treatment strategy for atypical subtrochanteric and femoral shaft fractures

Because of the propensity for delayed healing, the morbidity of these fractures is particularly high. The task force recognized that there are no controlled studies evaluating surgical treatment strategies for atypical subtrochanteric and femoral shaft fractures. The recommendations outlined here therefore are opinion-based and represent the consensus of the orthopedic surgeons who served on the task force. The task force developed a hierarchical approach to management that depends on whether the fracture is complete or incomplete.

History of thigh or groin pain in a patient on BP therapy. A femoral fracture must be ruled

out.[10,12,93,100,110,115,124,159] Anteroposterior and lateral plain radiographs of the hip, including the full diaphysis of the femur, should be performed. If the radiograph is negative and the level of clinical suspicion is high, a technetium bone scan or MRI of the femur should be performed to detect a periosteal stress reaction. The advantage of the technetium bone scan is that both legs will be imaged.

Complete subtrochanteric/diaphyseal femoral fracture. Orthopedic management includes stabilizing the fracture and addressing the medical management[10,12,93,100,110,115,124,159] (see below). Since BPs inhibit osteoclastic remodeling, endochondral fracture repair is the preferred method of treatment. Intramedullary reconstruction full-length nails accomplish this goal and protect the entire femur. Locking plates preclude endochondral repair, have a high failure rate, and are not recommended as the method of fixation. The medullary canal should be overreamed (at least 2.5 mm larger than the nail diameter) to compensate for the narrow intramedullary diameter (if present), facilitate insertion of the reconstruction nail, and prevent fracture of the remaining shaft. The proximal fragment may require additional reaming to permit passage of the nail and avoid malalignment. The contralateral femur must be evaluated radiographically, including scintigraphy or MRI, whether or not symptoms are present.[110]

Incomplete subtrochanteric/femoral shaft fractures. Prophylactic reconstruction nail fixation is recommended for incomplete fractures accompanied by pain.[10,12,93,100,110,115,124,159] If the patient has minimal pain, a trial of conservative therapy, in which

weight bearing is limited through the use of crutches or a walker, may be considered. However, if there is no symptomatic and radiographic improvement after 2 to 3 months of conservative therapy, prophylactic nail fixation should be strongly considered because these patients may progress to a complete fracture. For patients with incomplete fractures and no pain, weight bearing may be continued but should be limited and vigorous activity avoided. Reduced activity should be continued until there is no bone edema on MRI.

Medical management of atypical subtrochanteric/femoral shaft fractures

There are also no controlled studies evaluating medical treatment strategies for atypical subtrochanteric and femoral shaft fractures. The recommendations outlined here therefore are opinion-based and represent the consensus of the clinicians who served on the task force. The task force considered two main aspects of medical management:

Prevention. Decisions to initiate pharmacologic treatment, including BPs, to manage patients with osteoporosis should be made based on an assessment of benefits and risks. Patients who are deemed to be at low risk of osteoporosis-related fractures should not be started on BPs. For patients with osteoporosis in the spine and normal or only moderately reduced femoral neck or total-hip BMD, one could consider alternative treatments for osteoporosis, such as raloxifene or teriparatide, depending on the severity of the patient's condition. It is apparent that therapy must be individualized and clinical judgment must be used because there will not always be sufficient

evidence for specific clinical situations. BP therapy should be strongly considered to protect patients from rapid bone loss and increased fracture rates associated with clinical scenarios such as organ transplantation, endocrine or chemotherapy for breast or prostate cancer, and initiation of aromatase inhibitors and GCs. However, long-term BP therapy may not always be necessary in these clinical conditions.[160,161] More research is needed to determine the most effective dose and duration of BPs in patients with secondary causes of rapid bone loss.

The optimal duration of BP treatment is not known. Based on studies with alendronate[162] and risedronate,[163,164] patients with osteoporosis will have an antifracture benefit for at least 5 years. However, continued use of BP therapy beyond that time should be reevaluated annually, assessing factors such as BMD, particularly in the hip region, fracture history, newly diagnosed underlying conditions or initiation of other medications known to affect skeletal status, and new research findings in a rapidly evolving field. For those who are considered to remain at moderately elevated fracture risk, continuation of BP therapy should be strongly considered. Recent or multiple fractures (including asymptomatic vertebral fractures on lateral DXA imaging or lateral spine X-ray at the time of reevaluation) should suggest assessment or reassessment for underlying secondary causes and reevaluation of the treatment plan. Such patients are known to be at high risk of future fracture, and thus discontinuation of osteoporosis treatment is inadvisable. However, whether continuing BPs beyond 5 years will reduce that risk is unclear. In the FLEX trial, the incidence of clinical (but not

morphometric) vertebral fractures was significantly lower in those on 10 years of continued alendronate versus those who stopped after 5 years[162]; reduction in nonvertebral fracture incidence was limited to women without a fracture history but with femoral neck T-scores that were –2.5 or less.[165] While conclusions from this trial need to be tempered by its limitations, primarily the small study sample, these are the only long-term fracture data available with alendronate treatment. With regard to risedronate, 7 years of therapy did not further reduce the incidence of vertebral fractures below that observed with 3 and 5 years of therapy.[163] Models to help determine absolute risk of fracture in patients who have already been treated for 4 to 5 years are needed to help guide these decisions.

Based on current case reports and series, the median BP treatment duration in patients with atypical subtrochanteric and femoral shaft fractures is 7 years. For patients without a recent fracture and with femoral neck T-scores greater than –2.5 after the initial therapeutic course, consideration may be given to a "drug holiday" from BPs. Because some patients with atypical femoral fractures while on BPs were on concomitant therapy with GCs, estrogen, tamoxifen, or PPIs, continued BP therapy should be reevaluated, particularly in those deemed to be at low or only modestly elevated fracture risk. Whether discontinuation of BPs after 4 to 5 years in the lower-risk group will lead to fewer atypical subtrochanteric fractures is not known.

If BPs are discontinued, there are no data to guide when or whether therapy should be restarted. However, patients should be followed by clinical

assessment, bone turnover markers, and BMD determination. Restarting osteoporosis therapy, either with BPs or with a different class of agent, can be considered in patients who appear to be at increasing fracture risk. Models to help assess risk in previously treated patients, after 1 or more years off therapy, are needed to help guide these therapeutic decisions. It seems apparent that there can be no general rule and that decisions to stop and/or restart therapy must be individualized.

More than half of patients reported with atypical femoral fractures have had a prodrome of thigh or groin pain before suffering an overt break. Thus it is important to educate physicians and patients about this symptom and for physicians to ask patients on BPs and other potent antiresorptive agents about thigh or groin pain. Complaints of thigh or groin pain in a patient on BPs require urgent radiographic evaluation of both femurs (even if pain is unilateral). If plain radiographs are normal or equivocal and clinical suspicion is high, MRI or radionuclide scintigraphy should be performed to identify stress reaction, stress fracture, or partial fracture of either femur. Other disorders, such as forms of osteomalacia, also should be considered.[2]

Medical management. For patients with a stress reaction, stress fracture, or incomplete or complete subtrochanteric or femoral shaft fracture, potent antiresorptive agents should be discontinued. Dietary calcium and vitamin D status should be assessed, and adequate supplementation should be prescribed. A few case reports and anecdotal findings suggest that teriparatide therapy can improve or hasten healing of these fractures.[13,123] Additionally, consistent with a

large body of animal data,[166] some clinical evidence[167,168] indicates that teriparatide benefits nonunion of fractures, although a controlled trial in patients with Colles' fracture showed little effect.[169] Given the relative rarity of atypical femoral fractures and ethical issues surrounding potential randomization to placebo, it seems unlikely that there will be a randomized, controlled trial of teriparatide for subtrochanteric and femoral shaft fractures. Therefore, the level of evidence for efficacy likely will remain low. However, in the absence of evidence-based approaches, teriparatide should be considered in patients who suffer these fractures, particularly if there is little evidence of healing by 4 to 6 weeks after surgical intervention.

Summary and Conclusions

BPs are highly effective at reducing the risk of spine and nonspine fractures, including typical and common femoral neck and intertrochanteric fractures. However, there is evidence of a relationship between long-term BP use and a specific type of subtrochanteric and femoral shaft fracture. These fractures are characterized by unique radiographic features (ie, transverse or short oblique orientation, absence of comminution, cortical thickening, stress fracture or stress reaction on the symptomatic and/or contralateral side, and delayed healing) and unique clinical features (ie, prodromal pain and bilaterality). The apparent increased risk for atypical femoral fractures in patients receiving GCs is a concern because BPs are the mainstay for prevention of GC-induced osteoporotic fractures. Bone biopsies from the iliac crest and/or fracture site generally show reduced bone formation consistent with BP action.

Paradoxically, some patients show biopsy evidence of enhanced bone resorption. Biochemical BTMs are often normal but may be increased. These fractures can occur in patients who have not been treated with BPs, and their true incidence in both treated and untreated patients is unknown. However, they appear to be more common in patients who have been exposed to long-term BPs, usually for more than 3 years (median treatment 7 years). It must be emphasized that these fractures are rare, particularly when considered in the context of the millions of patients who have taken BPs and also when compared with typical and common femoral neck and intertrochanteric fractures. It also must be emphasized that BPs are important drugs for the prevention of common osteoporotic fractures. However, atypical femoral fractures are of concern, and more information is urgently needed both to assist in identifying patients at particular risk and to guide decision making about duration of BP therapy. Physicians and patients should be made aware of the possibility of atypical femoral fractures and of the potential for bilaterality through a change in labeling of BPs. Given the relative rarity of atypical femoral fractures, to facilitate future research, specific diagnostic and procedural codes should be created for cases of atypical femoral fractures, an international registry should be established, and the quality of case reporting should be improved. Research directions should include development of animal models, increased surveillance, and additional epidemiologic data to establish the true incidence of and risk factors for this condition and studies to address their surgical and medical management.

Disclosures

The American Society for Bone and Mineral Research (ASBMR) is well served by the fact that many of those responsible for policy development and implementation have diverse interests and are involved in a variety of activities outside the Society. The ASBMR protects itself and its reputation by ensuring impartial decision making. Accordingly, the ASBMR requires that all ASBMR officers, councilors, committee chairs, editors-in-chief, associate editors, and certain other appointed representatives disclose any real or apparent conflicts of interest (including investments or positions in companies involved in the bone and mineral metabolism field), as well as any duality of interests (including affiliations, organizational interests, and/or positions held in entities relevant to the bone and mineral metabolism field and/or the ASBMR).

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Relationship key: (1) Research grant or financial support from commercial entities; (2) consultant or member of advisory board to a commercial entity; (3) participant in a speakers' bureau; (4) employment or executive positions in pharmaceutical, medical device, or diagnostic companies, including industry scientists in the bone and mineral field; (5) stock holdings in pharmaceutical, medical device, or diagnostic companies; (6) any other situation or transaction in which you have a formal role or interest (eg, you serve on a bone-related organization's board, committee, or journal; a family member contracts with ASBMR; etc.).

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The American Society for Bone and Mineral Research (ASBMR) is the premier professional, scientific, and medical society established to promote excellence in bone and mineral research and to facilitate the translation of that research into clinical practice. The ASBMR has a membership of nearly 4000 physicians, basic research scientists, and clinical investigators from around the world. The ASBMR has a hard-earned reputation for scientific integrity.

Most of the Society's revenue comes from membership dues, fees paid to attend the Society's annual meeting, and subscriptions to ASBMR publications. Like many scientific, professional, and medical organizations, ASBMR also accepts grants from pharmaceutical companies, the federal government, and other entities to support its mission. ASBMR receives corporate support in the form of unrestricted educational grants from pharmaceutical companies, rental of exhibit space at its annual

meeting, and paid advertisements in its journal. To ensure that the Society adheres to the highest ethical practices, ASBMR has an ethics committee, consults with experts in health care ethics, and periodically reviews its practices with regard to managing potential conflict of interest.

Although task force members were required to disclose their potential conflicts of interest and their disclosures are published with this document, ASBMR recognizes that this might not go far enough to demonstrate to some that the final output of the task force is free of all bias. In an effort to address this concern, two additional individuals were assigned to the Atypical Femoral Fractures Task Force—an ethicist and a scientist knowledgeable about the musculoskeletal system who does not work directly on osteoporosis or bisphosphonates or with pharmaceutical companies who make or market bisphosphonates. The role of these individuals was to provide ethical oversight to the work of the task force. Both individuals have verified and attested that they witnessed no commercial bias during the task force's deliberations, during discussions with the pharmaceutical industry, or in the preparation of the final document by the task force.

[Conflicts Table Omitted]

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[Exhibit 45 to Ecklund Declaration]

ORIGINAL ARTICLE

Low-Energy Femoral Shaft Fractures Associated With Alendronate Use

Andrew S. Neviaser, MD, Joseph M. Lane, MD, Brett A. Lenart, BS, Folorunsho Edobor-Osula, MD, MPH, and Dean G. Lorich, MD

Objective: Increasing evidence suggests long-term alendronate use may overly suppress bone metabolism, limiting repair of micro-damage and creating risk for insufficiency fractures. The purpose of this study is to demonstrate an association between alendronate use and a specific pattern of low-energy femoral shaft fracture.

Design, Setting, and Patients: A retrospective review was performed of patients with femoral shaft fractures admitted to a Level 1 trauma center between January 2002 and March 2007. Seventy low-energy fractures were identified.

Main Outcome Measure: The medical records were reviewed, and the incidence and duration of alendronate use were recorded. The incidence of a specific femoral shaft fracture in those patients taking alendronate compared with those not being treated was determined.

Results: There were 59 females and 11 males. The average age was 74.7 years. Twenty-five (36%) were being treated with alendronate. None of the patients had used or were using other bisphosphonates. Nineteen (76%) of these 25 patients demonstrated a simple, transverse fracture with a unicortical beak in an area of cortical hypertrophy. This fracture pattern

was seen in only 1 patient (2%) not being treated with alendronate. Alendronate use was a significant risk factor for the fracture pattern (odds ratio [OR]) 139.33, 95% CI [19.0–939.4], $P < 0.0001$). This pattern was 98% specific to alendronate users. The average duration of alendronate use in those with the pattern was significantly longer than those who did not exhibit the pattern but were taking alendronate, 6.9 years versus 2.5 years of use, respectively ($P = 0.002$). Only 1 patient with the fracture pattern had been taking alendronate for less than 4 years.

Conclusions: Low-energy fractures of the femoral shaft with a simple, transverse pattern and hypertrophy of the diaphyseal cortex are associated with alendronate use. This may result from propagation of a stress fracture whose repair is retarded by diminished osteoclast activity and impaired microdamage repair resulting from its prolonged use.

Key Words: alendronate, osteoporosis, insufficiency fractures, subtrochanteric fracture, femur fractures, bisphosphonates

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Dr. Joseph M. Lane is on the Speaker's Bureau for the following: Novartis, Lilly, Proctor & Gamble, Sanofi-Aventis, and Rosche/GSK. There are no other financial disclosures to report. Reprints: Joseph M. Lane, MD, Osteoporosis and Metabolic Bone Disease Service, 535 E. 70th Street, New York, New York, 10021 (e-mail: lanej@ hss.edu).

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INTRODUCTION

Alendronate has been widely and successfully used to treat osteoclast-mediated metabolic bone diseases, such as osteoporosis. It has been proved effective in improving all clinical measures of osteoporosis, including increasing bone-mineral density, reducing laboratory markers of bone turnover, and reducing the number of fractures in the spine and long bones.[1,2] Alendronate targets osteoclasts by binding to the inorganic component of bone. Bound alendronate is released during resorption and endocytosed by osteoclasts. Once inside the cell, alendronate inhibits the mevalonate pathway for cholesterol synthesis and induces osteoclast apoptosis.[3] Bone resorption and remodeling rates are diminished as a result of osteoclast death. The sequelae of long-term alendronate use on bone metabolism, however, remain unclear. Studies in experimental animals treated with alendronate demonstrate reduced bony repair and accumulation of microdamage, leading to reduced bone toughness.[4,5] Odvina and Goh have each reported on patients sustaining low-energy fractures after prolonged therapy.[6,7] They warn that prolonged treatment with alendronate may lead to adynamic, fragile bone. We have empirically recognized a number of patients, treated with alendronate, who have sustained fractures of the proximal femoral shaft after minimal or no trauma. These fractures are characterized by a simple, transverse pattern, beaking of the cortex on one side, and hypertrophy of the diaphyseal cortex (Fig. 1). We retrospectively reviewed all low-energy sub-trochanteric and midshaft femur fractures admitted to our Level 1 trauma center in the last 5 years. We hypothesized

that this specific femoral shaft fracture is associated with long-term alendronate use.

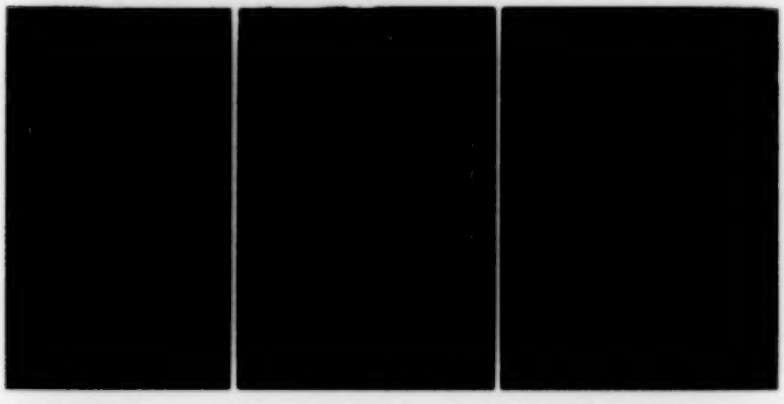

FIGURE 1. Representative radiographs of femoral shaft fractures sustained from minimal trauma in patients taking alendronate. Although each radiograph demonstrates the pattern in its entirety, we have highlighted the following features. A, Fracture pattern pictured with an arch measuring 30 degrees to highlight transverse nature. B, The arrow pointing out the unicortical beak C, Hypertrophied cortices outlined.

PATIENTS AND METHODS

After approval from the internal review board, a retrospective review was undertaken of all low-energy subtrochanteric and midshaft femur fractures admitted to a Level 1 trauma center between January 2002 and March 2007. Potential patients were identified through ICD-9 codes 820.2 through 821.01, inclusive. All AO Type 32, as well as Type 31 A3, fractures that involved or extended distally to the lesser trochanter, were eligible for inclusion. Low-energy fractures were defined as those caused by the equivalent to a fall from a standing height or less, as

documented in the medical record. Fractures caused by higher-energy trauma (motor vehicle accidents, falls from greater heights, blunt trauma, etc) or by bone tumors, either metastatic or primary, were excluded. Fractures at or beyond the distal third of the femoral shaft (AO Type 33) and pertrochanteric (Type 31 A1–2) were also excluded. Seventy low-energy fractures below the lesser trochanter and above the distal one third of the diaphysis were identified. The medical records were reviewed, and the incidence and duration of alendronate use were recorded. Confirmation of alendronate use and duration was obtained via phone contact with patients or their primary medical doctor. Two experienced attending orthopaedic surgeons and 1 orthopaedic resident independently reviewed the injury radiographs of these patients on 2 separate occasions. Each observer was blinded to patient characteristics, including alendronate use. The reviewers were asked to identify fractures that had a simple, transverse, or short oblique pattern in areas of thickened cortices with a unicortical beak. There was no communication among reviewers. The radiographs were shown in a computer-based slide presentation to each reviewer separately. The order of the radiographs was random and changed between the 2 sessions. Fleiss's and Cohen's kappa coefficients for interobserver and intraobserver agreement, respectively, were calculated by comparing the proportion of agreement in relation to the agreement as a result of chance. Kappa values of less than 0.40 indicate poor agreement, whereas values greater than 0.81 indicate near-perfect agreement. Risk estimates for association of bisphosphonate use and the fracture

pattern were represented as odds ratios (OR) with 95% confidence intervals (CI)

RESULTS

There were 59 females and 11 males. Baseline characteristics are described in Table 1. The average age was 74.7 years. Of the patients, 25 (36%) were being treated with alendronate. We were able to contact 15 patients and 3 primary care physicians to confirm alendronate use in 18 of the 25 patients (72%) being treated. We confirmed the duration of use in 16 of these patients (64%). All patients who were contacted confirmed the record to be accurate. None of the patients had used or were using other bisphosphonates. None of the males were being treated with alendronate.

A total of 31 patients (44%) had a diagnosis of osteoporosis, Of the 25 patients being treated with alendronate, 21 had been diagnosed with osteoporosis (84%). The 4 patients who had not been documented as having osteoporosis in the medical record did not have any other condition typically treated with alendronate. Ten patients had a diagnosis of osteoporosis but had not been treated with alendronate or any other antiresorptive medications. Breakdown of all described subgroups is summarized in Figure 2.

TABLE 1. Baseline Characteristics for Patients With Low-Energy Femoral Shaft Fractures (Differences Between Means for Patients Receiving Alendronate Treatment, Those Receiving Alendronate With Characteristic x-ray Pattern, and Those not Receiving Alendronate Treatment Were Calculated Using the Student's *t*-test)

	Age	Race	History of Osteoporosis (%)
All	74.4	68 W, 2 A	44.3
Female	76.5	57 W, 2 A	50.8
Male	63.5	11 W	9.1
Alendronate	69.4*	23 W, 2 A	34.0
Female	69.4	23 W, 2 A	34.0
Male	—	—	—
Nonalendronate	77.1	45 W	22.2
Female	81.4	34 W	26.4
Male	63.5	11 W	9.1
Alendronate + x-ray	69.5†	17 W, 2 A	84.2
Alendronate − x-ray	69.4	6 W	83.3

W, white; A, Asian; + x-ray, patients with characteristic x-ray pattern; − x-ray, patients without characteristic x-ray pattern.

*P = 0.002 for age of bisphosphonate versus nonbisphosphonate.

†P = 0.005 for age of bisphosphonate + x-ray vs nonbisphosphonate.

Fifty of the fractures were subtrochanteric, and 20 were located in the femoral shaft. Further classification is provided in Figure 3. The reviewers identified 20 patients with a simple, transverse, or short oblique pattern in areas of thickened cortices with a unicortical beak, represented in Figure 1. Nineteen of the 25 (76%) patients taking alendronate exhibited this fracture pattern. One patient of the 45 not taking alendronate (2.2%) was identified as having the fracture pattern. This patient was diagnosed with multiple myeloma several years after her fracture but had no lesions on her injury radiographs. Thus, 19 of 20 patients identified as having the fracture pattern were taking alendronate (95%). Alendronate use was a significant risk factor for having the fracture pattern in question (OR 139.33, 95% CI [19.0–939.4], $P < 0.0001$). This pattern was 98% specific to alendronate users. Identification of the fracture was consistent.

The interobserver kappa coefficient was 0.93. Intraobserver kappa values ranged from 0.87 to 1.0.

The duration of alendronate use was established in 16 patients and averaged 6.2 years (range 1–10 years). Ten of these patients demonstrated the fracture pattern. Six did not. Of the 6 patients who were taking alendronate but did not exhibit the pattern, the average duration of alendronate use was 2.5 years. This was significantly shorter compared with the 10 patients who had the fracture pattern (average 6.9 years of use, $P = 0.002$). There were no differences in age, race, body mass index (BMI), or osteoporosis history between these groups or among the entire study population.

The fracture pattern was not present in the 10 untreated patients with osteoporosis. No significant difference was found in the mean BMI of those taking and those not taking alendronate. The patients taking alendronate were, on average, younger than those not taking the drug by 8.9 years, but this difference was not significant.

DISCUSSION

The treatment of osteoporosis remains a highly successful intervention for reducing fractures in the elderly. Alendronate was the first oral bisphosphonate available in the United States and remains the most common antiresorptive medication used in treating this disease. The Fracture Intervention Trial, a multicenter randomized control study, demonstrated that alendronate reduced the risk of clinically significant fractures by more than 50% compared to placebo.[1]

We identify a fracture that is specific to patients being treated with alendronate and tends to occur after use of more than 4 years. Fractures associated with alendronate were AO type 32 A3 (simple, transverse). A unicortical beak was typically present, and the diaphyseal cortex was hypertrophied. Although we have not established a causal relationship, the association is sufficiently strong to consider alendronate's effect on bony metabolism when treating these patients.

The clinical utility of recognizing this fracture is recognition of the underlying pathophysiology that led to the fracture. The proximal femoral shaft is an area subject to high stress and would not be expected to fracture from minimal trauma without underlying metabolic bone pathology, such as osteoporosis. The fracture pattern was not seen in the 11 untreated patients with osteoporosis, suggesting that osteoporosis alone is not sufficient to cause this specific failure of the femoral shaft. Further investigation is needed to determine if alendronate is indeed the cause of this fracture. However, reports of insufficiency fractures in patients taking alendronate and studies in experimental animals suggest that adynamic metabolism from impaired resorption may be the underling pathophysiology that leads to these fractures.[4–9]

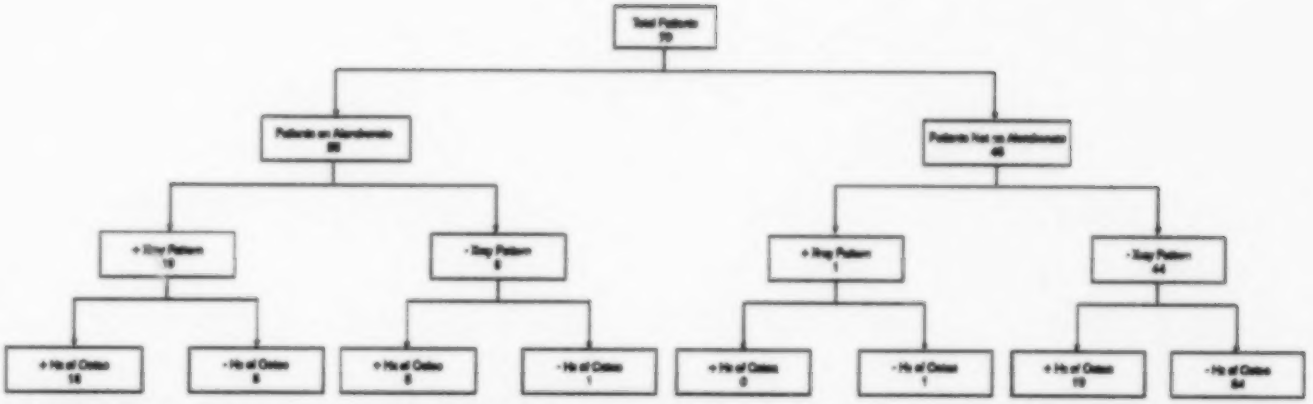

FIGURE 2. Subgroup breakdown of patients in the analysis. *+ x-ray pattern*, patients with presence of the x-ray pattern; *– x-ray pattern*, patients without presence of the x-ray pattern; *+ Hx of osteo*, patients with a history of osteoporosis; *– Hx of osteo*, patients without a history of osteoporosis.

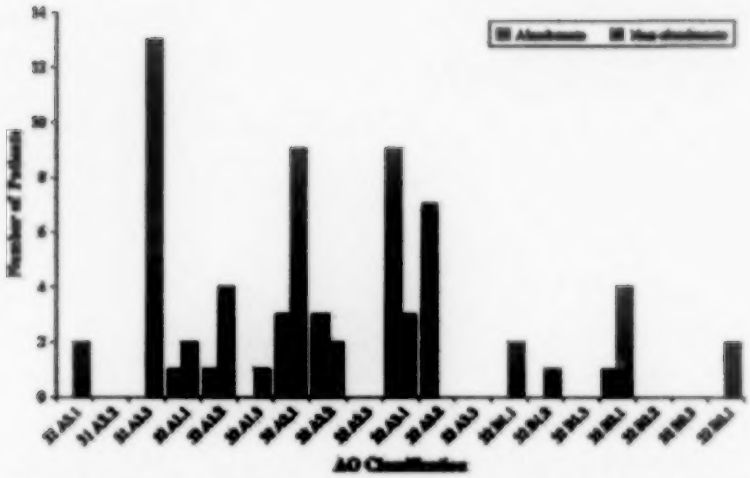

FIGURE 3. Classification of femoral shaft fractures. All 70 fractures were classified based on the Muller AO classification. Gray bars represent patients taking alendronate; black bars represent patients not taking alendronate. 32A3.1 and 32A3.2 represent simple, transverse subtrochanteric and midshaft fractures, respectively. 31A3.3 represents intertrochanteric fractures that extend into the subtrochanteric region.

In 2005 Odvina et al reported on 9 patients who had sustained spontaneous, nontraumatic, nonpathologic fractures while receiving prolonged alendronate therapy (longer than 3 years).[7] All 9 were engaged in normal activities of daily living, such as walking, standing, or turning around, at the time of fracture. Fracture sites included the pubic ramus, femoral shaft, ischium, rib, and sacrum. Six of these patients displayed either delayed healing or histomorphometric evidence of severely suppressed bone turnover. The bone surface was virtually devoid

of cellular elements, bone formation rate was reduced, and matrix formation was severely impaired. The authors raised the possibility that severe suppression of bone turnover may develop during long-term alendronate therapy, resulting in increased susceptibility to, and delayed healing of, nontraumatic, nonpathologic fractures. Studies in experimental animals treated with alendronate have demonstrated reduced repair and accumulation of microdamage in bone, as well as impaired fracture healing.[4,5,8,9]

Goh et al recently reported on 13 subtrochanteric insufficiency fractures over a 10-month period, 9 of which were in patients being treated with alendronate.[6] Eight of the 9 fractures had a pattern similar to what we describe and were associated with the cortical hypertrophy. The patients taking alendronate were younger and more active than those not being treated. They also reported prodromal thigh pain in 5 patients.

We have expanded on this case series by demonstrating a statistically significant association between alendronate use and this type of low-energy femur fracture. The simple transverse pattern, cortical hypertrophy, and prodrome of pain suggest that this injury may result from propagation of a stress fracture, which patients with suppressed microdamage repair are unable to heal. Minimal trauma is then required to produce a complete fracture. Optimal treatment will likely need to address the depressed bone metabolism. Further investigation is needed to validate the role of osteobiologics and anabolic osteoporosis agents in

these patients, both of which would theoretically appear to be important components of treatment.

Alendronate is an appropriate and highly successful first-line therapy for postmenopausal osteoporosis. This study was done to highlight a potential consequence of long-term therapy that may not be unique to alendronate. The potential for suppression of repair exists for all bisphosphonate drugs and may only be apparent with alendronate because it has been available for the longest time and is the most widely used.

This study carries all the shortcomings of a retrospective review. Using the medical record as the gold standard for determining alendronate incidence and use, as well as fracture mechanism, holds some inherent inaccuracy. This inaccuracy was minimized by contacting those patients taking alendronate. The uniform agreement between these patients and the record demonstrates that the record is accurate.

In conclusion, we describe a fracture pattern of the femoral shaft that is specific for patients being treated with alendronate. This fracture is characterized by (1) a simple, transverse pattern; (2) beaking of the cortex on one side; (3) hypertrophied diaphyseal cortices; and (4) resulting from minimal or no trauma. These fractures may be a consequence of alendronate use and its impact on bony metabolism, although further investigation is necessary.

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No. 17-290

IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,

Petitioner,

v.

DORIS ALBRECHT, ET AL.,

Respondents.

On Writ of Certiorari
To The United States Court of Appeals
For The Third Circuit

JOINT APPENDIX (VOLUME II OF II)
(Pages 400–771)

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C. Odvina et al., *Severely Suppressed Bone Turnover: A Potential Complication of Alendronate Therapy*, J. Clinical Endocrinology & Metabolism
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[Exhibit 47 to Ecklund Declaration]

Subtrochanteric insufficiency fractures in patients on alendronate therapy

A CAUTION

We carried out a retrospective review over ten months of patients who had presented with a low-energy subtrochanteric fracture. We identified 13 women of whom nine were on long-term alendronate therapy and four were not. The patients treated with alendronate were younger, with a mean age of 66.9 years (55 to 82) *vs* 80.3 years (64 to 92) and were more socially active. The fractures sustained by the patients in the alendronate group were mainly at the femoral metaphyseal-diaphyseal junction and many had occurred after minimal trauma. Five of these patients had prodromal pain in the affected hip in the months preceding the fall, and three demonstrated a stress reaction in the cortex in the contralateral femur.

Our study suggests that prolonged suppression of bone remodelling with alendronate may be associated with a new form of insufficiency fracture of the femur. We believe that this finding is important and indicates the need for caution in the long-term use of alendronate in the treatment of osteoporosis.

Alendronate is a potent inhibitor of bone resorption and was the first drug of its class to be approved for

use in the prevention of osteoporotic fractures by the USA Food and Drug Administration in 1995.[1] In two randomised controlled studies, treatment with alendronate has been shown to decrease the incidence of vertebral and femoral-neck fractures in post menopausal osteoporotic patients.[2,3] We also prescribe it as a first-line treatment for patients with osteoporosis. There are now a considerable number of patients who have been taking alendronate for at least five years. The medication is excluded from health-service subsidy and the full cost has to be borne by the patient. It is thus only really available to the upper socioeconomic classes

We have observed an apparent rise in the number of subtrochanteric fractures of the femur in women aged between 50 and 70 years after minimal or no trauma. Many of these patients had been receiving alendronate for at least three years.

We considered that it was unusual for patients receiving alendronate to sustain such fractures so easily. In an attempt to establish if there is a link between the two we reviewed all low-energy subtrochanteric fractures presenting to our department over a period of ten months, and compared the patients who were taking alendronate or had been taking it within one year of a fracture, with those who were not.

Patients and Methods

Between 1 May 2005 and 28 February 2006 we carried out a retrospective review of the operating records of all orthopaedic surgeons from two hospitals (Singapore General Hospital and Changi General Hospital, Republic of Singapore) to identify patients

who had been treated surgically for subtrochanteric fracture of the femur. A subtrochanteric fracture was defined as one in the region of the femur which extended from the lesser trochanter to the junction of the proximal and middle third of the femoral shaft. We included only fractures sustained in low energy trauma and excluded those due to a car accident, a fall from a height or underlying malignancy. Ethical approval was obtained from the Institutional Review Board before the study was commenced.

We identified 13 women with a subtrochanteric fracture which had been sustained by low-energy trauma. Details of the patients are given in Table I. There were nine women who had been taking alendronate, and four who had not. The patients in the alendronate group were younger, with a mean age of 66.9 years (55 to 82) *vs* 80.3 years (64 to 92).

Case records of the patients were reviewed to determine the mechanism of injury, the presence or absence of prodromal pain before the fracture, the bone mineral density (BMD) if available, the past medical history, the histological findings of bone from the site of the fracture when available, and the administration of alendronate within a year of the fracture. Radiographs were reviewed by three authors (S-KG, JSBK, TSH) to classify the patterns of the fracture according to the AO classification (Table II)[4], and to look for abnormality in the contralateral limb. There was complete agreement on all classifications. When necessary, the patients were also interviewed by telephone to ascertain the details of their symptoms and pharmacological history.

Table I. Details of the 13 patients

	Alendronate	No alendronate
Number	9	4
Mean age in yrs (range)	66.9 (55 to 82)	80.3 (64 to 92)
AO classification of subtrochanteric fracture		
A	8	0
B	1	3
C	0	1
Mean duration of alendronate therapy in yrs (range)	4.2 (2.5 to 5)	-

Table II. Comprehensive AO classification of subtrochanteric fractures[4]

Type	Description
A	Simple transverse or short oblique fracture
B	Comminution in the form of a medial or lateral wedge fragment
C	Severe comminution representing a segmental loss of continuity

Measurements of bone density. Bone density data were only available for some of the patients within a year either prior to, or after the fracture. The measurements were made by dual-energy x-ray absorptiometry (DEXA). Measurements were performed on the femoral neck and L1 to L4 vertebral bodies. The World Health Organisation defines osteoporosis as a BMD value more than 2.5 SDs below that of the young adult peak BMD known as the *T* score.[5] Osteopenia is defined as a BMD between 1.0 SD and 2.5 SDs below the young adult peak BMD.[5]

Results

The mean follow-up from the time of admission for the fracture was 223 days (99 to 341).

Mechanisms of injury. The mechanisms of injury are given in Table III. Four patients in the alendronate group reported that the fracture had occurred in the absence of a fall. Each of them recalled experiencing a sharp pain or hearing a snapping sound at the moment of fracture.

Prodromal symptoms. In the alendronate group five patients reported experiencing pain or discomfort in the fractured limb, between two and six months before the injury, one of whom had prodromal pain in the groin on the fractured side, whereas the remainder localised the pain at the lateral aspect of the thigh. By contrast, none of the patients in the nonalendronate group had prodromal symptoms.

History of treatment with alendronate. Nine patients were taking alendronate and oral calcium for treatment of osteoporosis either at the time, or within the year before the injury. Of the four patients who were not currently taking alendronate, two were taking oral calcium supplements. The data concerning the administration of alendronate, and the BMD of the patients (when available) are given in Table IV.

Fracture configurations. In the alendronate group eight of the patients had AO type-A fractures occurring at the metaphyseal-diaphyseal junction while the ninth had a type-B fracture. In six, cortical hypertrophy was identified on the lateral, tension side of the subtrochanteric region of the femur (Figs 1 and 2). In three, a similar hypertrophied cortex could be seen in the contralateral subtrochanteric region (Fig. 3).

Three patients in the non-alendronate group had an AO type-B fracture and one a type-C fracture (Fig. 4)

As judged on the plain radiographs, the bones appeared to be extremely osteoporotic with the loss of the trabecular pattern.

Histological findings. In five patients in the alendronate group, bone biopsies were sent intra-operatively for histological analysis to exclude neoplasia. All were found to be benign.

No histological specimens were sent from the four patients who were not taking alendronate because there was radiological evidence of severe osteoporosis in each.

Discussion

Pauwels[6] was the first to identify that the subtrochanteric region of the femur is subjected to maximal bending movement. As such, this area is one of the strongest parts of the femur and it is unlikely to fail in low-energy trauma, unless extreme osteoporosis is present. It has been estimated that only 10% to 34% of all fractures of the hip are in the subtrochanteric region.[7]

The patients in the alendronate group were striking for several reasons. All had received alendronate and oral calcium therapy for a mean of 4.2 years (2.5 to 5), the trauma which these nine patients had sustained was minimal, a few had experienced prodromal pain in the months preceding the fracture and lastly, most were in the early stages of the menopause and had led relatively active lifestyles at the time of injury.

Table III. Biomedical data and mechanism of injury in all 13 patients

Case	Age (yrs)	Mechanism	Co-morbidities	Presence and duration of prodromal pain
Alendronate				
1	65	Tripped and fell	Alpha thalassaemia minor, hysterectomy and ovariectomy	Yes, 2 months
2	60	Heard a crack in the thigh while retrieving a shot during badminton	Nil	Yes, 6 months
3	67	Fell down three stairs and landed on buttocks	Nil	No
4	55	Right anterior thigh pain after tripping awkwardly while crossing road	Eczema, on long-term oral steroids	No
5	69	Heard a crack while shopping	Diabetes mellitus. Cervical and lumbar spondylosis	Yes, 2 months
6	82	Right hip pain after fall	Supraventricular tachycardia Mycoplasma pneumonia	Yes, 6 months
7	68	Slipped and fell on to buttocks	Hysterectomy and ovariectomy. Cervical and lumbar spondylosis	Yes, 3 months
8	64	Fractured femur while walking down stairs	Nasopharyngeal carcinoma 10 years previously Pseudohypoparathyroidism	No
9	71	Tripped and fell while shopping	Ischaemic heart disease Osteoarthritis knees	No
No alendronate				
1	92	Fell after vertiginous episode	Hypertension. Hypothyroidism	No
2	64	Tripped and fell while walking	Hypotension, renal failure and osteodystrophy Diabetes mellitus	No
3	86	Fell after being pushed by grandson	Peptic ulcer disease. Patellofemoral arthritis	No
4	79	Slipped and fell in kitchen	Nil	No

Table IV. The bone mineral density (BMD) status of the alendronate patients and the duration of treatment at the time of the injury

	BMD				
Case	Year of DEXA scan	Left femoral neck T-score	Lumbar spine T-score	Diagnosis	Alendronate duration (yrs)
1	2003	-1.1	-0.8	Osteopenia	4
2	-	-	-	Osteoporosis	2.5
3	2003	-1.6	-1.2	Osteopenia	3
4	2005	-2.1	-1.1	Osteopenia	5
5	2005	-1.3	-1.2	Osteopenia	5
6	-	-	-	-	at least 5
7	-	-	-	Osteoporosis	at least 5
8	2005	-2.1	-2.5	Osteoporosis	5
9*	-	-	-	-	3

* unable to give details of BMD status

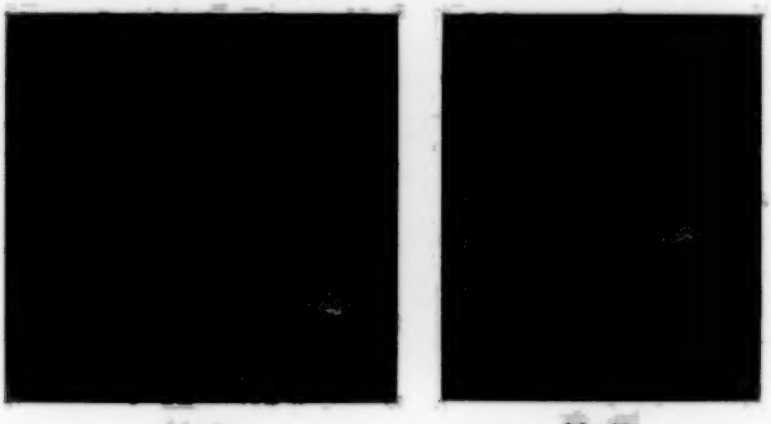
Alendronate belongs to the family of bisphosphonate drugs which are stable synthetic analogues of pyrophosphate characterised by a phosphorous-carbon-phosphorus bond.[8] The administration of bisphosphonates, as a group, is one of the first-line treatments for the prevention of osteoporotic fractures in menopausal patients.[9] The Fracture Intervention Trial[2] study showed that patients who were taking alendronate had a reduced risk of sustaining an osteoporotic fracture at a follow-up of three years. It has also been proven that alendronate therapy is associated with an increase in BMD in osteoporotic patients.[10] This effect was sustained throughout the duration of alendronate therapy when administered for up to ten years.[10]

Alendronate inhibits bone resorption by suppressing the activity of osteoclasts, and inducing them to undergo apoptosis.[8] While this leads to an increase in the BMD of patients with osteoporosis,[11] treatment with alendronate has also been shown to reduce the amount of bone turnover.[12,13] In animal experiments concern has been expressed that alendronate therapy can lead to the accumulation of skeletal microdamage.[14] In humans, prolonged administration of intravenous pamidronate can lead to the development of osteopetrosis or marble bone disease.[15] This microdamage may increase the risk of insufficiency fractures.

The fractures in the alendronate group were all simple, mostly AO type-A subtrochanteric fractures in patients who had radiologically good cortical bone stock. This contrasts with the radiological findings seen in patients who were not taking alendronate. It is interesting that thickening in the lateral femoral

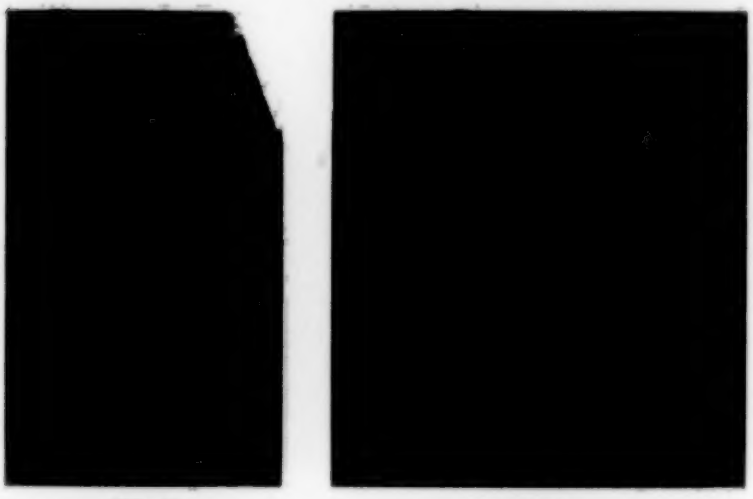
cortex was present in six of the alendronate patients, and in three of these the cortical thickening was bilateral. This, and the history of prodromal pain, lend support to the possibility that these were insufficiency fractures which possibly resulted from altered bone metabolism.

This is the first report to document a series of fractures in the subtrochanteric region of the femur in patients who were receiving alendronate for a long period. However, our study certainly does not establish cause and effect. Indeed, many of these patients were originally on alendronate and calcium therapy because they were at a higher risk for osteoporotic fractures. Nevertheless, our findings identify a potential, originally unrecognised, side-effect of prolonged pharmacological suppression of bone turnover.

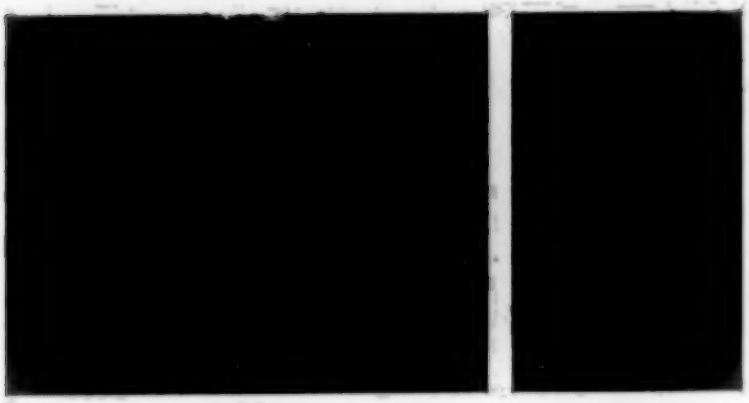


Radiographs of a 65-year-old woman who had tripped and fallen while walking on flat ground and had been

on alendronate for the past five years, showing a) a type-A left subtrochanteric fracture with b) a cortical reaction in the lateral (tension) side of the femur.



Radiographs of a 69-year-old woman with a history of cervical and lumbar spondylosis and who had bilateral thigh pain for two months before the fracture. She had been on alendronate for five years. She heard a snapping sound in a) her right thigh while shopping. b) The left lateral subtrochanteric region shows evidence of a stress injury.



Radiographs of a 67-year-old woman who had fallen down three steps and landed on her buttocks, showing a) anteroposterior view of a subtrochanteric fracture with a transverse configuration and a medial sharp spike, and b) the right subtrochanteric region showing cortical hypertrophy on the lateral side. She had been on alendronate for three years.

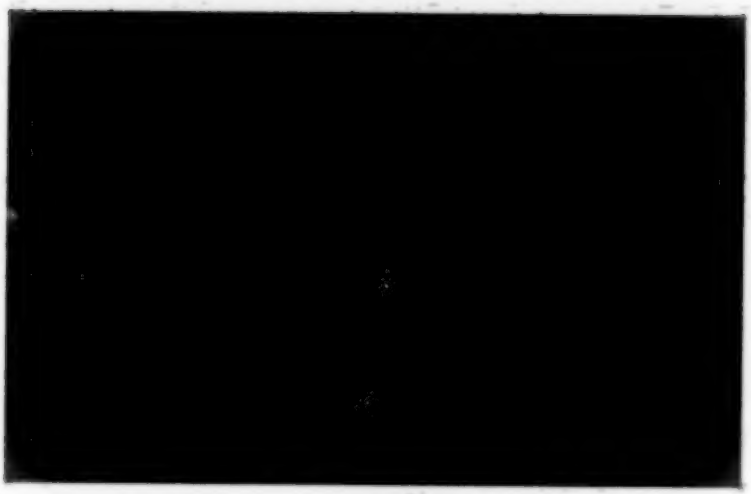


Fig. 1

A 92-year-old woman with chronic vertigo, hypothyroidism and hypotension who had a vertiginous fall and was found to be hyponatraemic and septic on admission. Radiograph showing a type-C subtrochanteric fracture. She was not taking alendronate.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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[Exhibit 48 to Ecklund Declaration]

Severely Suppressed Bone Turnover: A Potential Complication of Alendronate Therapy

Clarita V. Odvina, Joseph E. Zerwekh, D. Sudhaker Rao, Naim Maalouf, Frank A. Gottschalk, and Charles Y. C. Pak

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Alendronate, an inhibitor of bone resorption, is widely used in osteoporosis treatment. However, concerns have been raised about potential oversuppression of bone turnover during long-term use. We report on nine patients who sustained spontaneous nonspinal fractures while on alendronate therapy, six of whom displayed either delayed or absent fracture healing for 3 months to 2 yr during therapy.

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Abbreviations: BFR, Bone formation rate; BMD, bone mineral density; BsAP, bone-specific alkaline phosphatase; GIO, glucocorticoid-induced osteoporosis; NTx, N-telopeptide; SSBT, severe suppression of bone turnover.

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Histomorphometric analysis of the cancellous bone showed markedly suppressed bone formation, with reduced or absent osteoblastic surface in most patients. Osteoclastic surface was low or low-normal in eight patients, and eroded surface was decreased in four. Matrix synthesis was markedly diminished, with absence of double-tetracycline label and absent or reduced single-tetracycline label in all patients. The same trend was seen in the intracortical and endocortical surfaces.

Our findings raise the possibility that severe suppression of bone turnover may develop during long-term alendronate therapy, resulting in increased susceptibility to, and delayed healing of, nonspinal fractures. Although coadministration of estrogen or glucocorticoids appears to be a predisposing factor, this apparent complication can also occur with monotherapy. Our observations emphasize the need for increased awareness and monitoring for the potential development of excessive suppression of bone turnover during long-term alendronate therapy. (*J Clin Endocrinol Metab* 90: 1294–1301, 2005)

ALENDRONATE, A POTENT inhibitor of bone resorption, is now widely used in the treatment of osteoporosis. A number of randomized clinical trials have shown that it significantly increases bone density of spine and hip and reduces the incidence of fractures in osteoporotic patients (1–4).

Although alendronate is generally safe and effective, it carries the potential risk of

oversuppressing bone turnover that can potentially impair some of the biomechanical properties of bone. In experimental animals, alendronate has been shown to inhibit normal repair of microdamage arising from marked suppression of bone turnover, which, in turn, results in accumulation of microdamage (5–7). A 2- to 7-fold increase in microdamage accumulation after pharmaceutical suppression of bone remodeling was associated with a 20% reduction in bone toughness (the ability to sustain deformation without breaking), without reduction in bone strength (6–8). However, the clinical significance of these changes in biomechanical measurements has not yet been well defined.

In addition to microdamage accumulation, chronic oversuppression of bone turnover by alendronate may allow secondary mineralization to continue (9), producing hypermineralized bone that may be more brittle (10, 11). The degree of mineralization has been shown to affect the material properties of bone, with low mineralization levels (as seen in osteomalacia) causing reduced stiffness and strength, and hypermineralization likely contributing to reduced fracture toughness (10, 11).

Ott (12) speculated that chronic alendronate therapy in humans might impair mechanical strength of bone. This suggestion was based on the apparent increase in fracture rate with prolonged therapy (2), though challenged by the authors of that report (13). Recently, Whyte *et al.* (14) described a 12-yr-old boy who, after 3 yr of treatment with iv bisphosphonate (pamidronate), presented with findings consistent with osteopetrosis, *i.e.* increased bone density and impaired remodeling. The authors, however,

acknowledged that the dose of pamidronate given to the patient was more than four times the amount typically given to children with osteogenesis imperfecta.

In this report, we describe bone biopsy data from nine patients with osteoporosis or osteopenia treated with alendronate for 3–8 yr alone or in combination with estrogen. All patients had spontaneous nonspinal fractures that developed after 1–8 yr of alendronate treatment. Histomorphometric analysis of bone biopsy samples revealed a marked suppression of bone turnover.

Subjects and Methods

Patients

Nine patients (eight postmenopausal women and one man) on longterm alendronate treatment were included in this report. Four patients (patients 1–4) were from the Henry Ford Hospital in Detroit, and five (patients 5–9) were from the University of Texas Southwestern Medical Center in Dallas. Alendronate was given at a dose of 10 mg/d or 70 mg/wk for 3–8 yr along with supplemental calcium. Eight patients were also given vitamin D, 400–800 IU/d, whereas one patient was maintained on a pharmacological dose of vitamin D. Relevant clinical data are summarized in Table 1.

In patients 1–4, alendronate was given alone, without estrogen or glucocorticoid (group A, Table 1). Patients 1–3 were postmenopausal women without prevalent fractures, in whom alendronate treatment was started elsewhere because of either osteoporosis or osteopenia by bone density. Patient 4 was started on alendronate when he presented with metatarsal

stress fractures and was found to have osteopenia by bone density.

In patients 5–7 (group B, Table 1), alendronate was administered with estrogen. Patients 5 and 7 took estrogen continuously for 12 and 15 yr, respectively, whereas patient 6 received it intermittently for 3 yr. Although none had prevalent fractures, alendronate was started elsewhere for postmenopausal osteoporosis (patients 5 and 6) or osteopenia (patient 7) of spine or hip by bone density.

Patients 8 and 9 were given alendronate for glucocorticoid-induced osteoporosis (GIO; group C, Table 1). Patient 8 has been taking glucocorticoid for asthma for 20 yr, and patient 9 for fibromyalgia for 8 yr, before alendronate was begun. Glucocorticoid was continued during and after alendronate was stopped in patient 9 and was tapered and eventually discontinued in patient 8. Patient 9 was on vitamin D, 50,000 IU thrice a week, for postsurgical hypoparathyroidism. Both women had fractures of the femoral shaft and metatarsal bones after minimal trauma before alendronate treatment.

Nonspinal fractures during alendronate therapy

All nine patients developed atraumatic nonspinal fractures while on alendronate treatment (Table 1) and while performing normal daily activities such as walking, standing, or turning around. Among the seven patients who were not on glucocorticoid (patients 1–7), atraumatic nonspinal fractures (sacrum, rib, ischium, pubic rami, femoral shaft) developed after 3–8 yr of alendronate treatment. One patient (patient 2) also had a lumbar vertebral fracture. Among those with GIO, patient 8 developed

a separation of previously formed callus of the fractured femoral shaft 1 yr after starting alendronate. Patient 9 fractured the right femoral shaft, at the site of a previous fracture, while walking, after 2 yr of alendronate treatment.

Because the patients continued taking alendronate after the fracture(s), we had the opportunity to radiographically assess fracture healing while still on treatment (Table 1). In six patients (patients 3 and 5–7 without glucocorticoid, and patients 8 and 9 on glucocorticoid), evidence of delayed fracture healing (lack of adequate callus formation and filling in of fracture gap) was observed 3 months to 2 yr after fracture occurrence in the ischium, pubic rami, and femoral shaft. In one (patient 8), delayed healing of the femoral fracture persisted for 2 yr despite internal fixation and bone graft. In the remaining patients (patients 1, 2, and 4), fracture healing could not be assessed because bone biopsy was obtained shortly after the incident fractures.

Bone biopsy

The decision to perform bone biopsy was based on the unusual clinical presentation of these patients. First, the fracture sites (*e.g.* bilateral femoral shaft, pubic bone, ischium) were not the typical sites for osteoporotic fractures. Second, a majority of these patients (patients 1–7) were fracture-free in the intervening years before the presentation. Last, six of nine patients (patients 3 and 5–9) presented with delayed fracture healing. After obtaining an informed consent, bone biopsies were performed while patients were still on alendronate therapy (3–8 yr) and about 1 month to 2 yr after incident fractures (Table 1).

A transiliac bone biopsy was obtained using a 7.5-mm diameter trocar under local anesthesia, following *in vivo* double-tetracycline labeling as previously described (15). A 2-10-4-4 labeling regimen with declomycin was used in Dallas, and a 3-11-3-4 regimen with oxytetracycline was used for the patients at the Henry Ford Hospital. Specimens were prestained for 72 h in Villanueva, Osteochrome (Polysciences, Inc., Warrington, PA). After dehydration in increasing concentrations of alcohol, the specimens were embedded in methylmethacrylate and kept at 37 C until fully polymerized. The embedded biopsy samples were then sectioned on a Reichert-Jung model E microtome (Cambridge Instruments, Heidelberg, Germany) at a thickness of 10 μm. A total of six sequential sections were cut from each specimen. Sections 1, 3, and 5 were mounted directly to slides and were examined under UV light for tetracycline uptake. Sections 2, 4, and 6 were mounted to slides, deplasticized in xylene, stained with toluidine blue, and examined for static measurements. Histomorphometric measurements were made with an Aus Lena microscope video camera, and an image capture program (Bioquant Bone Morphometry Program; R & M Biometrics, Nashville, TN). Histomorphometric measurements and calculations were based on modifications of previously published methods (16–18). The bone formation rate (BFR) was calculated as half of the single-labeled surfaces plus all the double-labeled surfaces multiplied by mineral apposition rate in $\mu m^3/\mu m^2/d$ (19). When no double-labeled surfaces were observed, BFR was calculated as half of the single-labeled surfaces multiplied by 0.3 μm / d as previously described (19). The nomenclature

of the measured and calculated variables is according to the criteria established by the Committee on Bone Histomorphometry of the American Society for Bone and Mineral Research (20). Slides, both for fluorochrome assessment and toluidine blue stained for static measurements, were analyzed by a single investigator (J.E.Z.) at the University of Texas Southwestern Medical Center, who was blinded to the patients' identity. For patients in whom no tetracycline double labels were observed, all three cut sections were examined for the presence of any tetracycline labeling.

Biochemical measurements and bone densitometry

Laboratory studies were done either on the day of, or shortly before, bone biopsy. In some patients, not all tests could be obtained. Serum samples were assayed for calcium, phosphorous, creatinine, PTH (ELISA kit; Alpco Diagnostics, Windham, NH), 25-hydroxyvitamin D (ELISA, Alpco Diagnostics), bone-specific alkaline phosphatase (BsAP=Alkphase-B; Quidel, Mountain View, CA), and osteocalcin (Oc, ELISA; Diagnostic Systems Laboratories, Webster, TX). Urine was collected in 24-h pools for calcium, creatinine, N-telopeptide (NTx, Osteomark; Ostex International, Seattle, WA), and hydroxyproline (OH-pro, Hypro nosticon; Organon Teknika Corp., Durham, NC). Spot fasting urine samples were used for the analysis of NTx and creatinine in patients 1–4. Except for serum calcium, phosphorous, and creatinine, the remaining serum and urine analyses from all patients were performed at the Mineral Metabolism laboratory in Dallas.

TABLE 1. Clinical data

Patient	Age (yr)/ sex	Diagnosis	Duration of alendronate treatment (yr)	Other medications	Incident fractures (yr on alendronate)	Delayed/absent healing on alendronate (fracture site)	Fracture healing pattern (months off alendronate)
Group A							
1	55/F	PO	6	Ca, D	Sacrum (6)	NA	No (12)
2	70/F	PO	7	Ca, D	Vertebra, rib (7)	NA	Yes (6)
3	53/F	POpm	8	Ca, D	Femoral shaft (8)	4 months (femoral shaft)	No (9)
4	69/M	IO	8	Ca, D	Bilateral femoral shaft (8)	NA	No (8)
Group B							
5	69/F	PO	3	Et, Ca, D	Sacrum, ischium (3)	3 months (ischium)	Yes (8)
6	70/F	PO	5	Et, Ca, D	Pubic rami (3)	2 yr (pubic rami)	Yes (4)
7	67/F	POpm	5	Et, Ca, D	Bilateral femoral shaft (5)	9 months (left femoral shaft)	Yes (5)
Group C							
8	49/F	GIO (asthma)	3	Prednisone, Ca, D	Proximal femur (1)	2 yr (femur)	No (8)
9	64/F	GIO (fibromyalgia)	4	Prednisone, Ca, D	Metatarsal, proximal femur (3)	8 months (proximal femur)	Yes (3)

PO, Postmenopausal osteoporosis; POpm, postmenopausal osteoporosis; IO, idiopathic osteoporosis; Et, estrogen; Ca, calcium; D, vitamin D; NA, not available or not applicable; F, female; M, male.

TABLE 2. Histomorphometric findings in cancellous bone

	Patient									Control (mean ± SD)
	1	2	3	4	5	6	7	8	9	
BV/TV (%)	14.3	15.2	14.7	9.7	9.4	12.3	17.3	10.9	8.9	21.2 ± 4.9
OV/BV (%)	0.42	0.68	0.17	0.07	0	0	2.5	0.69	0.05	1.95 ± 1.07
O.Th (μm)	4.3	8.0	4.6	4.5	0	0	10.2	4.0	3.9	9.3 ± 2.1
Ob.S/BS (%)	1.7	0	0.14	0	0	0	0.7	3.6	0.3	4.4 ± 2.0
ES/BS (%)	3.5	9.3	9.3	5.6	0.9	2.1	4.3	1.3	1.7	4.9 ± 2.0
Oc.S/BS (%)	1.0	0.3	0.35	0.13	0	0.2	0.35	0.3	0.1	0.7 ± 0.7
dLS/BS (%)	0	0	0	0	0	0	0	0	0	4.3 ± 2.9
aLS/BS (%)	0.6	0	0.42	0.44	0	0	0.5	0	0.3	6.0 ± 4.1
BFR ($\mu m^3/\mu m^2/yr$)	1.0	0	0.7	0.2	0	0	0.6	0	0.4	15 ± 9.8

BV, Bone volume; TV, total volume; OV, osteoid volume; Ob.S, osteoblastic surface; ES, eroded surface; Oc.S/BS, osteoclastic surface/bone surface; dLS, double-label tetracycline label; aLS, single tetracycline label. BFR, Bone formation rate calculated as ½ × aLS/BS × MAR (micrometers per day) obtained from cortical double-labeled surfaces as previously described (19). BFR for four patients was calculated as ¼ × aLS/BS × 0.3 μm/d as previously described (19).

Bone mineral density (BMD) of L2–L4 vertebrae, femoral neck, and distal third of the radius was measured by dual-energy x-ray absorptiometry (Hologic QDR, Waltham, MA). Selected x-rays and bone scans were obtained to confirm the presence of fractures and to determine the status of fracture healing (callus formation and filling in of fracture gap).

Results

Bone histomorphometry

Quantitative bone histomorphometric findings of the cancellous bone are summarized in Table 2. Bone volume was reduced in all patients, but the most striking finding was severe depression of bone formation with absence of double-tetracycline labeling in all nine patients (Fig. 1, A and B). Five of the nine biopsy specimens revealed occasional single tetracycline labels (patients 1, 3, 4, 7, and 9). The mean calculated BFR was almost 100-fold lower than in healthy postmenopausal women (Ref. 16; see Table 4). In seven patients (patients 2–7 and 9), cancellous bone surfaces were quiescent with minimal, or no, identifiable osteoblasts (Fig. 2, A and B). Osteoid thickness and volume were either normal or reduced, excluding the possibility of osteomalacia. In addition, there was a trend toward low bone resorption; osteoclastic surface was low or low-normal, except in patient 1, who received alendronate without estrogen, and eroded surface was also reduced in four patients (patients 5, 6, 8, and 9).

All patients had decreased intracortical osteoid surface (Table 3A). Osteoblast surface was also reduced except in patient 1. Five patients (patients 2,

3, 5, 6, and 8) displayed low osteoclast and eroded surfaces. The same trend was observed for endocortical surface, with reduced osteoid and osteoblast surfaces in all patients. Osteoclast surface was low, except in three (patients 2, 4, and 7), and eroded surface was reduced except in four (patients 1–4). Dynamic parameters were also markedly reduced for both intracortical and endocortical bone surfaces, although a greater reduction was seen at the endocortical bone surfaces (Table 3B).

Table 4 summarizes the mean values for the different histomorphometric measurement at the three bone compartments (cancellous, endocortical, and intracortical bone surfaces) compared with control subjects. Except for the intracortical osteoclast surface, all the surface and dynamic parameters were significantly lower in the patients with severe suppression of bone turnover (SSBT) compared with the published controls. The mean BFR at the three bone surfaces was 30- to 100-fold lower than the corresponding values in healthy controls (15).

FIG. 1. A, Photomicrograph under UV light from patient 5, showing absence of double label (*yellow arrow*). B, Photomicrograph under UV light from a normal subject, showing two distinct areas of double

label with tetracycline. The faint inner label is from the first course of tetracycline (*yellow arrow*), and the more prominent outer label is from the course of tetracycline given 10 d later (*orange arrow*).

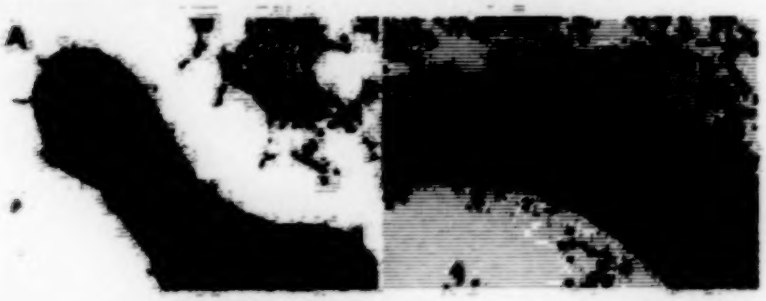

FIG. 2. A, Trabecular bone from patient 5, showing absence of surface osteoid, osteoclasts, and osteoblasts (×160). B, Trabecular bone from a normal subject, showing abundant osteoid (*black arrow*), surface osteoclasts (*yellow arrow*), and osteoblasts (*red arrow*) (×160).

Laboratory findings at the time of bone biopsy

Serum calcium, phosphorus, creatinine, 25-hydroxyvitamin D, and PTH were within the reference range (Table 5). Although serum BsAP ranged widely, serum Oc was either low or at the lower limit of the reference range. Urinary NTx was low to midnormal in seven and high-normal in two. Urinary OH-pro was low or low-normal in all five patients in whom it was measured.

BMD before and after alendronate therapy

BMD results before the initiation of alendronate therapy, obtained from outside institutional records, were limited. Among the six postmenopausal women

not on glucocorticoids, four had osteoporosis and two had osteopenia when alendronate treatment was begun. Among four patients with osteoporosis, the T-score of at least one site was still in the osteoporotic range (below –2.5 SD) in two patients (patients 2 and 6) but was in the osteopenic range (–1.0 to more than –2.5 SD) in two patients (patients 1 and 5) after alendronate treatment (Table 5). Among two with osteopenia, patient 7 was no longer osteopenic, whereas data for patient 3 were unavailable. In patient 4, T-scores were reported to be in the osteopenic range before alendronate treatment and remained in the osteopenic range after treatment. Baseline BMD data were reportedly in the osteopenic range in the two patients on glucocorticoids, and both had normal BMD after 3–4 yr of alendronate treatment.

Fracture healing after stopping alendronate

Therapy was stopped after obtaining a bone biopsy in all patients. Assessment of fracture healing after discontinuation of treatment was available in all patients (Table 1). Four patients had delayed healing. Patients 1, 3, and 4, who were on alendronate alone, continued to have evidence of nonhealing fractures 12, 8, and 9 months off treatment, respectively, and patient 8 (GIO) continued to have poor fracture healing 8 months after discontinuation of alendronate. The remaining four patients had satisfactory fracture healing. In patient 2, fracture healing was noted at 6 months. In patient 5, callus formation was noted at 3 months, and a significant reduction in pain and improvement in mobility occurred after being off of treatment for 8 months. Patient 6 showed robust callus formation in the nonhealing pelvic fracture 4

mo.ıths after stopping alendronate, with associated improvement in pain. Patient 7 had evidence of fracture healing at 5 months associated with resolution of pain. In patient 9 (GIO), femoral shaft fracture showed complete healing at 3 months. None of the patients developed new fractures after alendronate was discontinued.

Discussion

We describe our clinical observations in nine unselected patients maintained on long-term alendronate therapy for osteoporosis/osteopenia who developed biopsy-proven SSBT. The universal presentation of these patients was spontaneous or atraumatic nonvertebral fracture(s), with delayed or nonhealing of fractures exhibited by six patients while still on alendronate, and by four patients after discontinuation of therapy.

All nine patients displayed histomorphometric evidence of SSBT, similar to the so-called adynamic bone or low turnover described in patients on chronic maintenance hemodialysis (21). The bone surfaces were virtually devoid of cellular elements, BFR was reduced, and matrix formation was severely impaired. In addition, bone resorption was reduced in most patients. Reduced rates of bone formation and resorption were also found on both intracortical and endocortical bone surfaces, indicative of a generalized involvement. To distinguish from adynamic bone, we refer to the condition described in this report as SSBT, defined histologically by reduced osteoblastic and osteoclastic surfaces with decreased or absent tetracycline labeling.

TABLE 3. Resorption and formation parameters on the intracortical and endocortical surfaces

	Patient									Control (mean ± SD)*
	1	2	3	4	5	6	7	8	9	
A. Intracortical surfaces										
OS/BS (%)	5.3	0.3	1.6	1.4	0	3.3	5.9	3.8	0.27	18.7 ± 7.9
Oc.S/BS (%)	11.8	0	0	0	0	2.2	0	1.4	0	5.86 ± 3.36
ES/BS (%)	4	0.22	2.8	7.5	0	0	7.5	0.9	2.9	6.39 ± 4.68
Oc.S/OS (%)	1.04	0.08	0.6	1.2	0	0	0.9	0.15	1	1.01 ± 0.79
dLS/BS (%)	3.5	0.2	0.6	0	0	1.1	0.14	1.4	0.2	
sLS/BS (%)	7.1	0.8	1.1	0	0	0	0.7	1.1	0.3	9.2 ± 4.9
MAR (μm/d)	1.0	0.5	1.0	0	0	0.8	0.6	0.7	0.8	0.65 ± 0.18
IRFR/BS (μm²/μm²/yr)	24.0	1.0	4.0	0	0	3.0	1.0	6.0	0.5	25.0 ± 15
B. Endocortical surfaces										
OS/BS (%)	12.1	0.86	1.5	1.4	0	0	3.9	2.2	0.74	24.4 ± 14.4
Oc.S/BS (%)	0.94	0	0	0	0	0	0	0	0	6.88 ± 7.86
ES/BS (%)	10.5	10.9	4.2	7.3	0.63	3.8	4	3.1	2.7	9.56 ± 6.21
Oc.S/OS (%)	0	1.7	0.5	1.0	0	0.33	1.27	0.58	0	1.41 ± 1.88
dLS/BS (%)	0	0	0	0	0	0	0	0	0	
sLS/BS (%)	0.6	0	0	0.2	0	0	0.5	0	0	12.5 ± 9.8
MAR (μm/d)	0	0	0	0	0	0	0	0	0	0.53 ± 0.14
IRFR/BS (μm²/μm²/yr)	0.3	0	0	0.1	0	0	0.3	0	0	35 ± 28

OS, Osteoid surface; BS, bone surface; Oc.S, osteoblastic surface; ES, eroded surface; Oc.S, osteoclastic surface; dLS/BS, double-labeled surface; sLS/BS, single-labeled surface; MAR, mineral apposition rate. Intracortical IRFR was calculated as (dLS/BS + ½ sLS/BS) × MAR; endocortical IRFR was calculated as ½ × sLS/BS × 0.3 μm/d (19).

* Refs. 15 and 16.

TABLE 4. Comparison of the mean values for selected histomorphometric measurements between patients and controls

	Cancellous bone		Endocortical surface		Intracortical surface	
	Patients	Control	Patients	Control	Patients	Control
OS/BS (%)	3.70 ± 5.09[c]	14.20 ± 6.80	2.53 ± 3.79[c]	24.40 ± 14.40	2.48 ± 2.92[c]	18.70 ± 7.90
Ob.S/BS (%)	0.70 ± 1.32[c]	4.40 ± 2.00	0.10 ± 0.31[c]	6.85 ± 7.85	1.71 ± 3.57[c]	5.88 ± 3.38
Oc.S/BS (%)	0.30 ± 0.39[c]	0.70 ± 0.70	0.00 ± 0.01[b]	1.41 ± 1.88	0.55 ± 0.50	1.01 ± 0.70
BFR ($\mu m^3/\mu m^2/yr$)	0.33 ± 0.57[c]	15.0 ± 0.80	0.00 ± 0.15[c]	25.0 ± 23.0	4.30 ± 7.85[c]	23.0 ± 15.0

Data are presented as mean ± SD. OS, Osteoid surface; BS, bone surface; Ob.S, osteoblastic surface; Oc.S, osteoclastic surface. Statistical significance vs. control group depicted as [b] $P < 0.01$; and [c] $P < 0.001$.

Clinically, SSBT was characterized by incident nontraumatic fractures involving the skeletal areas that are rich in cortical bone, with fractures usually occurring at atypical sites such as femoral shafts, pubic bone, and ischium. In addition, fracture healing appeared to be impaired in most patients with SSBT. Fracture healing was absent or incomplete in six patients, who continued alendronate therapy for 3 months to 2 yr after the onset of incident nonspinal fractures. When alendronate was stopped, fracture healing was still incomplete at 8–12 months in four patients.

There is some evidence that alendronate may have contributed to the histological and clinical picture of SSBT described above. Suppression of bone turnover, to the degree we encountered here, by bone histomorphometry is uncommon in untreated postmenopausal osteoporosis. Coadministration of estrogen has been shown to exaggerate suppression of bone turnover (22, 23), as was seen in three of our patients. However, fractures occurred at sites not typically seen in osteoporosis. Moreover, in some patients, the nonspinal fractures healed poorly while on alendronate, but healed satisfactorily after stopping treatment in most patients. Glucocorticoids alone could suppress osteoblastic bone formation, but sometimes increase osteoclastic resorption, a feature not seen in our two patients with GIO. Chronic steroid treatment in a patient with hypoparathyroidism (as in patient 9) may suppress both bone formation and resorption, but we are unaware of any report showing histomorphometric abnormality with nonspinal fractures.

Prior reports support the view that SSBT may be pathogenetically related to chronic bisphosphonate treatment. In experimental animals, alendronate can impair microdamage repair and compromise some of the biomechanical properties of bone (5–8). In humans, a clinical picture resembling socalled marble bone disease was described after intermittent iv pamidronate treatment (14). Based on an apparent increase in fracture rate after long-term alendronate treatment, a concern has previously been raised that alendronate might impair bone strength (12). More recently, osteonecrosis of the jaw requiring surgical removal of affected tissue was reported in 59 patients who had received iv bisphosphonate for malignancy and in seven patients who took oral bisphosphonate for osteoporosis (24). Although the mechanism was not clearly defined, low bone remodeling was cited as a possible cause of this condition. A recent article reported that alendronate given over a period of 10 yr was safe and effective (25). However, the nonvertebral fracture rate appeared to be numerically the same or higher (three and four women with nonvertebral facture/100 subject-year for the 10- and 5-mg groups, respectively) during the late period of alendronate treatment, compared with the early period (three women with fracture/100 subject-year), despite a higher bone density. Although this trial was not designed to test fracture efficacy, apparently no attempt was made to ascertain whether patients who sustained nonspinal fractures displayed evidence of impaired fracture healing. Overall, the above reports suggest that excessive suppression of bone turnover by bisphosphonate may affect biomechanical competence of bone (26).

Several factors may have contributed to the development of SSBT. One factor is concurrent diseases: GIO in two patients and postsurgical hypoparathyroidism in one patient. Both chronic glucocorticoid treatment (27) and parathyroid insufficiency (28) are known to reduce bone turnover and could have exaggerated the effect of alendronate. Thus, the nonspinal fractures appeared to develop sooner compared with the patients on alendronate alone (1–3 yr *vs.* 6–8 yr, respectively).

Another factor may have been concurrent estrogen therapy. Among six postmenopausal women with osteoporosis osteopenia, three were on both estrogen and alendronate, whereas three received alendronate alone. The onset of spontaneous fractures was earlier among patients on combination therapy, compared with those on monotherapy (3–5 yr *vs.* 6–8 yr), and the indices of bone resorption on bone biopsy tended to be lower in those taking estrogen. Thus, combination therapy with another antiresorptive agent, such as estrogen, might cause a more severe suppression of bone turnover (21, 22) and might have increased the potential for developing SSBT.

The third factor may be the duration of alendronate therapy. The skeletal half-life of alendronate is long (29), which could explain the residual effect on bone density 3 yr after withdrawal of the drug (30). It is therefore possible that the suppressive effect of this drug on bone resorption might be cumulative over time. Four patients in this report were treated with alendronate without estrogen or glucocorticoid; they developed spontaneous nonspinal fractures 6–8 yr after alendronate therapy, compared with 3–5 yr for

those taking alendronate with estrogen and 1–3 yr for patients who also received glucocorticoids.

We acknowledge that this report has some limitations and unanswered questions. First, the biochemical markers did not reveal as prominent a suppression of bone turnover as the histomorphometric indices. Most patients displayed low or low-normal urinary NTx, OH-proline, and serum Oc, but serum BsAP was inconsistent. The results are compatible with previous reports showing that alendronate may exert a more marked suppression (90–95%) of bone turnover at the tissue level (31) compared with only a 50% reduction from baseline in biochemical markers (32, 33). The discordance between the histomorphometric and biochemical markers of bone turnover could be related to the variable degree of suppression at different skeletal sites. Although bone histomorphometry reflects local bone turnover, the changes in biochemical markers are more reflective of changes in the whole skeleton. Another possible explanation is the effect of fractures on bone turnover. Development of fractures has been shown to significantly increase bone turnover markers (34). Last, the less impressive or inconsistent changes in biochemical markers of bone turnover may have been due to inherent analytical and biological variability of the assays. The key issue to consider is that the quantitative histomorphometric analysis, upon which we based the bone turnover state in the diagnosis of SSBT, is generally regarded as the gold standard for the assessment of bone turnover.

Second, the presentation of patient 1 appears to be somewhat different than in others. Serum BsAP and

urinary NTx were higher than in others, and osteoclastic and osteoblastic surfaces did not differ from the control group on the cancellous and intracortical bone surfaces. However, the patient shared many of the features of the other eight patients, both clinically and objectively, with BFR being markedly decreased on the cancellous and endocortical bone surfaces. It is possible that this case represents one end of the spectrum of varying degrees of bone turnover suppression manifested by SSBT.

Third, three of seven patients without GIO had the unusual occurrence of femoral shaft fractures. We offer no explanation for this finding except to note that the reduction in elastic modulus reported to occur during bisphosphonate treatment was more marked in cortical than in trabecular bone (35).

An important limitation of this report is the lack of a control group. Published randomized trials with alendronate showed that some patients developed nontraumatic appendicular fractures while receiving either alendronate or placebo (1–3). Thus, although arguments were presented earlier linking SSBT to bisphosphonate therapy, a definitive causal relationship cannot be made. It is also possible that the development of SSBT in the cases described in this report represents an atypical response to alendronate therapy. However, most of our patients demonstrated the expected treatment outcomes, at least in the first few years of therapy, such as a satisfactory rise in BMD. The absence of SSBT despite a substantial suppression of bone turnover in a previous bone histomorphometric study (31) might be a reflection of a relatively short duration of alendronate therapy of 2–3 yr. In our patients, nonspinal fractures did not

develop during the first 3–6 yr of treatment among those maintained on alendronate alone or with estrogen. Except for the two patients with GIO, we do not believe that there was an underlying condition that predisposed to the development of SSBT. Seven patients on alendronate alone or with estrogen did not have prevalent fractures. Vitamin D deficiency and osteomalacia were excluded as potential reasons for poor fracture healing.

Finally, we cannot infer from our observations whether SSBT is unique to alendronate or can also develop with other bisphosphonates. That all nine patients with SSBT described here took alendronate may simply reflect the longer availability and wider usage of this bisphosphonate.

In conclusion, our clinical experience suggests that alendronate can potentially cause SSBT, resulting in increased susceptibility to nonspinal fractures that heal poorly. This complication appears to occur earlier when alendronate is coadministered with either glucocorticoids or estrogen. However, it can also develop after treatment with alendronate alone if the treatment is prolonged. Our observation does not diminish the important role of alendronate in the management of osteoporosis. Rather, it emphasizes the need for awareness of this potential complication during therapy. Although biochemical markers of bone turnover appear to be of limited value, the onset of spontaneous nonspinal fractures, particularly of femoral shaft on alendronate treatment, should raise the level of suspicion for this complication. Additional studies are needed to determine how long bisphosphonates can safely be given.

Acknowledgments

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E-mail: clarita.odvina@utsouthwestern.edu.

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This study was presented, in part, at the 25th Annual Meeting of The American Society for Bone and Mineral Research, Minneapolis, MN, September 19–23, 2003.

None of the authors have any known conflict of interest in the conduct of this study.

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[Exhibit 70 to Ecklund Declaration]

To: Olivero, Kerin A.
<kerin_olivero@merck.com>

From: Goldberg, Michael R.
</O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=GOLDBERM>

Cc:

Bcc:

Received Date: 2005-08-03 13:06:22

Subject: FW: WAES0506USA01525 and WAES 0507USA01043 INCOMING SCANNING

Can you do a quick search to see if the doc mentioned below has ever submitted reorts inthe past?

Mike

Michael R. Goldberg MD, PhD
Clinical Risk Management and Safety Surveillance
484-344-2860
FAX 484-344-7920
michael_goldberg@merck.com

A Where patients come first

CRMSS - Monitoring the safety of our products

Our mission is to proactively assess and describe the safety profile of our products.

-----Original Message-----
From: Santora, Arthur C.
Sent: Tuesday, August 02, 2005 5:41 PM
To: Goldberg, Michael R.
Subject: RE: WAES0506USA01525 and WAES 0507USA01043 INCOMING SCANNING

Has the reported any Fx AEs in the past?
My NTx is 17 and I don't take anything. I'll talk to you tomorrow and try to be careful in the interim.

Art

-----Original Message-----
From: Goldberg, Michael R.
Sent: Tuesday, August 02, 2005 5:26 PM
To: Santora, Arthur C.
Subject: FW: WAES0506USA01525 and WAES 0507USA01043 INCOMING SCANNING

FYI. Let's discuss. Tomorrow between 1 and 4 should be good.

Mike

Michael R. Goldberg MD, PhD
Clinical Risk Management and Safety Surveillance

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michael_goldberg@merck.com

A Where patients come first

CRMSS - Monitoring the safety of our products

Our mission is to proactively assess and describe the safety profile of our products.

-----Original Message-----

From: Gundermann, Stephanie M.

Sent: Tuesday, August 02, 2005 3:03 PM

To: AER Mailbox

Cc: Goldberg, Michael R.

Subject: WAES0506USA01525 and WAES 0507USA01043 INCOMING SCANNING

Adverse Experience Reporting Telephone memo

WAES No.

0506USA01525

0507USA01043

Product Name

Fosamax* (alendronate sodium)

Adverse Experience(s): fractured thigh bone

Summary of Call:

On 02-AUG-2005, I phoned the office of **REDACTED** who returned my call.

WAES 0507USA01043 –

REDAC reported that he has 25 patients with long bone fractures who have taken Fosamax* (alendronate sodium) for a long time. He also reported that 100% of patients in his practice that have experienced femoral fractures (without being hit by a taxicab), were taking Fosamax* (alendronate sodium) for over 5 years. At New York Hospital they call it the "Fosamax Fracture". He stated that if a patient's Ntx marker goes down below 20, he switches them to risedronate (ACTONEL) and that attention should be paid to the Ntx and not the DEXA scan. He reported that biopsies of the bone show that the bone is asleep and there is a subset of people who are over-suppressed which is a small number in comparison to the number of hip fractures. **REDAC** is planning a study (with Cornell University) for 1 year to look at long bone fractures in patients who were treated with Fosamax* (alendronate sodium) versus a control group who was not. He referred to a publication by Dr. Charlie Pak, which describes similar experiences.

WAES 0506USA01525 –**REDAC** also reported that he had a patient in her 70's that was experiencing thigh pain and later twisted in a swimming pool with her grandchildren and broke her femur after taking Fosamax* (alendronate sodium) for 7 years. **REDAC** discontinued therapy with Fosamax* (alendronate

sodium), and switched the patient to (FORTEO). Subsequently, the patient slowly healed.

This was all the information provided by **REDAC**, so I thanked him and concluded my call.

AER Associate/Coordinator follow-up (check one):

Send all scheduled correspondence.

Cancel all scheduled correspondence.

v

Send Thank You only.

Other (describe):

Stephanie Gundermann
02-AUG-2005

AER Associate/Coordinator Name
Date

02-AUG-2005

Date(s) of Telephone Call

[Exhibit 71 to Ecklund Declaration]

To: Santora, Arthur C. <art_santora@merck.com>; Seebach, Frank <frank_seebach@merck.com>; Walters, Margaret <margaret_walters@merck.com>

From: Miteva, Yanna R </O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=MITEVAYA>

Cc: Bold, Thomas M. <thomas_bold@ merck.com>; Budzynski, Christina M. <christina_budzynski @merck.com>

Bcc:

Received Date: 2006-11-06 18:48:23

Subject: FW: AE reports of Brittle bones with Alendronate therapy

---

FYI, below is the query from Singapore regarding a local registry of cases of non-traumatic and/or non-healing fractures.

You will receive shortly an invitation for a teleconference with MSD Singapore where this issue will be further discussed.

Thank you.

Yanna

-----Original Message-----

From: Jen, Lai Hung

Sent: Tuesday, October 31, 2006 11:03 PM

To: Kilker, Diane M; Hostelley, Linda S; Bold, Thomas M.; Vilardo, Laura E

Cc: Lo, Thean Soo; Soon, Linda; Goh, Karen; Chin, Annie; Seah, Joleen

Subject: RE: AE reports of Brittle bones with Alendronate therapy
Importance: High

Hi All,

Please advise whether there is any criteria or SOP from a global perspective to set up a local registry.

If not, we will work internally and with local regulatory agency to discuss the need of a registry.

Regards
Lai

Lai Hung Jen, MD
Medical Director
Merck Sharp & Dahme (I.A.) Corp. Singapore
Tel. (65) 6296-7772
Fax. (65) 6296-0005
E-mail: laijen@merck.com

-----Original Message-----
From: Goh, Karen
Sent: Wednesday, October 18, 2006 6:48 PM
To: Kilker, Diane M; Hostelley, Linda S; Bold, Thomas M.; Vilardo, Laura E
Cc: Jen, Lai Hung; Lo, Thean Soo; Soon, Linda
Subject: RE: AE reports of Brittle bones with Alendronate therapy

[Business Confidential - Merck & Co., Inc. Whitehouse Station, NJ USA]

Dear Diane,

Hi. Thanks for your guidance and sharing. Based on this, we have sent the following WAES reports to HQ:

1) 0610SGP00001
2) 0610SGP00002
3) 0610SGP00003
4) 0610SGP00006
5) 0610SGP00007

and will send any others which may later appear in publication later.

With regards to our earlier question, we are interested to know if WPS has been seeing a significant number of fracture non-healing type of reports similar to ours and as described by Odvina, that might be a signal for a label update. This would be for our internal information and will not be shared with external parties. Thanks.

In our attempt to obtain follow up information, one of the doctors had suggested the creation of a local registry to track such cases. Would HQ be able to advise on the criteria for setting up a local registry as initiated by Merck? Is there an SOP for this? Would this be warranted in this case?

Would appreciate your input once again. Many thanks!

Best regards,
Karen Goh
Regulatory Affairs Associate
Merck Sharp & Dahme I.A. Corp, Singapore
Tel: +65-6393 7637
Fax:+65-6296 0005

-----Original Message-----
From: Kilker, Diane M
Sent: Saturday, October 14, 2006 4:10 AM
To: Hostelley, Linda S; Goh, Karen; Bold, Thomas M.; Vilardo, Laura E
Cc: Jen, Lai Hung; Lo, Thean Soo; Soon, Linda
Subject: RE: AE reports of Brittle bones with Alendronate therapy
Importance: Low

Hello Karen,

Your plan for data entry of these reports sounds reasonable. Unfortunately, until we are able to link the existing cases (and it sounds like this is unlikely), we leave them as separate reports without relating them. This also happens in the US where we suspect a duplicate but really cannot be certain. We leave the reports separate and attempt follow-up to ascertain specific identifiers. I don't see much else you could do at this time.

As for your question below, I will defer to our CRMSS group (Thomas Bold and Laura Vilardo) who are responsible for looking at the AE data in aggregate. Is there something specific you are looking for? I can confirm we have other cases in the WAES database as fracture non-healing has been noted in the literature (author Odvina). Please let Laura and Thomas know the specifics of your request unless a confirmation is all you needed.

Thomas and Laura, please see question below.

Kind regards,
Diane

-----Original Message-----
From: Hostelley, Linda S
Sent: Friday, October 13, 2006 7:01 AM
To: Goh, Karen; Kilker, Diane M; Bold, Thomas M.
Cc: Jen, Lai Hung; Lo, Thean Soo; Soon, Linda
Subject: Re: AE reports of Brittle bones with Alendronate therapy

---

Karen

Thanks for the information

Your plan for waes sounds good

Diane will send you detailed language and can also address your question re other reports

Best regards

Linda

-----Original Message-----

From: Goh, Karen
To: Hostelley, Linda S
CC: Jen, Lai Hung; Lo, Thean Soo; Soon, Linda
Sent: Fri Oct 13 05:46:15 2006
Subject: AE reports of Brittle bones with Alendronate therapy

---

Dear Linda,

Hi. We've recently come to know of a number of local cases of adverse experiences of brittle bones in patients who have been on Fosamax therapy and we thought to alert you on this in view of the number of cases and as some of these will be published in a journal.

Our medical services colleagues have spoken to 1 doctor (an orthopedic surgeon) who said that he knows of 8 of such cases (some from other colleagues). He reported the following for these 8 cases:

- all sub-trochanteric transverse fractures of the shaft
- slow healing observed
- all have been on alendronate therapy (estimated average 2–3 years of use)

- these patients have no other medical conditions of note
- some of the patients' BMDs did not show that they were osteoporotic
- hence, he expressed concern about the overuse of alendronate in the local environment
- elaborated on 1 specific case where there was no trauma involved. Prior to the fracture, the patient had complained of pain in both thighs. He saw a GP who did an X-ray of the femur which showed that it was ok. However, the next day, the patient sustained a fracture in both femurs just from getting up from sitting in a chair.
- he knew of these reports from various sources (2 are his own)
- 6 of these patients are relatives of doctors

We have tried to find out further information on each of these cases from this orthopedic surgeon, explaining our obligation to report these as AEs and to monitor the safety profile of our product. However, the surgeon is unwilling to report these AEs or provide further information pertaining to this. He is working with several other doctors to collect more cases before considering if they would publish their findings. This orthopedic surgeon also informed us that another of his colleagues will be publishing an article in the British Bone & Joint Surgery journal on another 10 similar cases. The article has apparently been accepted for publication and would be expected to be in print in a few months' time.

We will be able to enter the AE report for the 10 cases that will be in the British Bone & Joint Surgery publication when the article has been published. We will also be creating a WAES report for the 1 specific case described above. We can create another report for the other 7 generalized cases described above. However, we have recently also reported 3 similar cases in NWAEs (0610SGP00001-3) that was received by another orthopedic surgeon, and are unable to ascertain if these are amongst the 7 cases described above. In view of this, would WPS be able to advise how we should capture this in the WAES report, as we are concerned about duplicate reports and in view that the doctors are unwilling to report or provide further information and clarification?

Would we also be able to find out if WPS has received similar reports from other countries worldwide?

Please do let us know if you require further information and clarification on this! Many thanks!

Best regards,
Karen Goh
Regulatory Affairs Associate
Merck Sharp & Dahme I.A. Corp, Singapore
Tel: +65-6393 7637
Fax:+65-6296 0005

[Exhibit 102 to Ecklund Declaration]

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: FOSAMAX PRODUCTS :No.1:06-Md-01789
LIABILITY LITIGATION :JFK-JCF

- - -

CROSS NOTICED IN VARIOUS OTHER ACTIONS

- - -

CONFIDENTIAL INFORMATION —
SUBJECT TO FURTHER CONFIDENTIALITY REVIEW

- - -

May 7, 2008

- - -

Videotaped deposition of ARTHUR C. SANTORA, II, M.D., Ph.D., held in the offices of Hughes Hubbard & Reed, One Battery Park Plaza, New York, New York 10014, commencing at 10:08 a.m., on the above date, before Linda L. Golkow, a Federally-Approved Registered Diplomate Reporter and Certified Shorthand Reporter.

- - -

GOLKOW TECHNOLOGIES, INC.
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877.370.3377

* * *

Page 794

implied that Fosamax reduces the risk of fracture in women who don't have osteoporosis.

BY MR. O'BRIEN:

Q. I agree with you there. So, the FDA in this analysis, particularly in that sentence that Merck's counsel just read to you, the FDA just simply got it wrong; is that right?

A. No. The FDA did not get it wrong. I believe it's your interpretation that's wrong. If we had done what the reviewer considers disingenuous in pooling a treatment for a population in which the drug works with an effect of the drug in a population where it doesn't work, that would have been disingenuous. That's not what we did. We reported the data in this study looked at for a variety of different ways, noted that the drug did not reduce the risk of fracture in women who had not had either a fracture or low bone mineral density. That was included in both the

Page 795

clinical study report, and that's described in the labeling.

Q. So, based on —

It's my understanding, based on the clinical trial evidence that Merck had and presented to the FDA, Merck cannot say that for those patients without osteoporosis that the use of Fosamax prevents fractures, right?

MR. MARSHALL: Objection to the form, and now you've exceeded the scope of the redirect.

MR. O'BRIEN: This is my last question.

BY MR. O'BRIEN:

Q. Is that right?

A. Merck has stated that the drug works to reduce the risk of fracture in people who have osteoporosis defined as either vertebral fracture or defined as a low bone mineral density. Your question, I think, is related to whether we have promoted or stated the drug works in other populations to reduce the risk

of fracture. The answer is no, we have not indicated that Fosamax reduces the risk of fracture in women who don't have osteoporosis.

Q. Because there's no evidence that it does, right?

A. Right. There's no evidence that any drug reduces the risk of fracture in people who don't have osteoporosis.

MR. O'BRIEN: Thank you.

THE VIDEOTAPE TECHNICIAN:

We're going off the record. The time is 3:10 p.m. This is the end of tape 5.

- - -

(Whereupon, the deposition concluded at 3:10 p.m.)

- - -

CERTIFICATE

I, LINDA L. GOLKOW, a Notary Public and Certified Court Reporter of the State of New Jersey, do hereby certify that prior to the commencement of the examination, ARTHUR C. SANTORA, II, M.D., Ph.D. was duly sworn by me to testify to the truth, the whole truth and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a verbatim transcript of the testimony as taken stenographically by and before me at the time, place and on the date hereinbefore set forth, to the best of my ability.

I DO FURTHER CERTIFY that I am neither a relative nor employee nor attorney nor counsel of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not financially interested in the action.

_____

LINDA L. GOLKOW, CCR
Notary Number: 1060147
Notary Expiration: 1-2-11
CSR Number: 30X1176200

[Exhibit 113 to Ecklund Declaration]

To: Ross, Philip D. <rossph@NorthAmerica.msx.merck.com>

From: Stern, Lawrence S. <O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=STERNLAW>

Cc:

Bcc:

Received Date: 2001-10-25 20:45:01

Subject: FW: osteoporosis website - Susan Ott's opinions

Larry

-----Original Message----

From: Stern, Lawrence S.

Sent: Thursday, October 25, 2001 1:17 PM

To: Teutsch, Carol B; Yates, John; Kimmel, Donald B.; Krempasky, Marlene Y.; Lawler, Barbara J.

Subject: osteoporosis website - Susan Ott's opinions

Check it out

Susan Ott's Web site (Updated 4/16/01)

http://courses.washington.edu/bonephys/opbis.html#side

Alendronate deposits in the bone for over ten years, and will accumulate with use. Studies in beagles have shown that high doses result in accumulation of small

cracks in the bone and decreased mechanical strength. (Mashiba (2000). Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J Bone Mineral Res 15:613–620.)

Thus, I do not think it is wise to give alendronate for longer than 4.5 years. I would have to see definite proof of safety and benefit to the bones (in terms of fractures) before I would give it longer than that.

Estrogen is still my first choice for prevention of osteoporosis, because it has other benefits and a known safety record. In women already taking estrogen, alendronate causes only a slight increase in the bone density, so I do not recommend it unless the patient has demonstrated fractures or bone loss while on the estrogen, and has an elevated marker for bone resorption ...

Larry

[Exhibit 118 to Ecklund Declaration]

FINAL MEETING MINUTES July 15, 2008
June 27, 2008 MRL Osteoporosis Scientific Input Meeting

This document contains notes from the above-referenced June 27, 2008 consultants' meeting. It is not an attempt to create a transcript of the meeting or to include every thought or comment made at the meeting. Even if not indicated below, the external consultants did not agree with every comment made by others during the meeting.

Executive Summary

External Attendees: Felicia Cosman, David Dempster, Harry Genant, Joseph Lane, Michael McClung, Jeri Nieves, Regis O'Keefe, Robert Recker, Charles Turner[1]

Merck Attendees: Jim Adams, Julie Chandler, Anne de Papp, Donald Kimmel, Scott Korn, Graham Lumsden, Yanna Miteva, Fernando Osorio (MSD Spain), Arthur Santora Sharon Scurato, Ted Reiss

Key Summary Points:

1) Overall incidence of low energy subtrochanteric/femoral shaft fractures in the

---

[1] Dr. Mark Bolander from the Mayo Clinic was also invited to attend and present at this meeting, but cancelled due to illness. Several consultants were aware of Dr. Bolander's preliminary data, discussed at a separate meeting in May 2008, suggesting that bisphosphonate users are not at an increased risk of developing subtrochanteric fractures. The consultants agreed that Dr. Bolander's data on this issue is important and should be fully analyzed, published and considered by the medical community.

osteoporotic population is very low (a recent estimate was 6% of all femur fractures).

2) The recently available data do not alter the well established benefit of bisphosphonates to reduce fracture risk in osteoporotic patients.

3) There is no good evidence to suggest an increased incidence of low energy subtrochanteric/femoral shaft fractures in patients treated with bisphosphonates over background rates.

4) Causality has NOT been demonstrated.

5) In Dr. Lane's observational study, the proportion of patients with "simple transverse fractures" and "thick cortices" appears greater and the proportion with "complex spiral fractures" and "thin cortices" appears smaller in patients treated with bisphosphonates.

6) The morbidity and mortality associated with the "simple transverse" fractures of the proximal femur is usually *less* than that with spiral fractures of the femur.

7) There was general agreement that bisphosphonates do not lead to cortical thickening, only prevention of cortical bone loss.

8) The consultants cautioned about hypothesizing on mechanism prior to establishing if there is an increased risk.

9) Many of the consultants thought that suggesting that low energy subtrochanteric/femoral shaft fractures occur in bisphosphonate users because of "oversuppression" of bone turnover was not appropriate as there has been no demonstration that reduction of bone remodeling in patients with these

atypical fractures was any greater than that seen in bisphosphonate treated patients in general.

10) There are no published case series with controls that would allow assessment of risk of subtrochanteric / femoral shaft fractures associated with bisphosphonate treatment. The only case study (Lænart, Lane et al, unpublished, abstract presented as a poster at the 2007 ASBMR scientific meeting) has significant limitations including potential referral bias, and inability to match cases with controls with similar osteoporosis severity, and other risk factors for fractures (e.g., glucocorticoid use). The fractures reported were low trauma fractures and the frequency of stress fractures (typically about 10% of all low-trauma fractures in the elderly) was not studied.

11) Studies to delineate the epidemiology of subtrochanteric / proximal femoral shaft fractures are required prior to a study of treatment-related risk of these rare fractures.

Scientific Questions Posed to Consultants and Consultant Comments:

What is a low energy fracture of the femur?

A low energy fracture of the femur is defined as one that occurs from a fall from standing height or less. Stress fractures are included in the larger group of low energy fractures.

What is the definition of a stress fracture?

Stress fractures are defined as fractures occurring with either normal or increased activity, but without an identifiable traumatic event. Characteristic clinical features of incomplete (unicortical) stress fractures of long bones include point tenderness or

pain on weight bearing at the site of fracture. Incomplete stress fractures may be diagnosed acutely with MRI, within several days with Tc-99m MBP bone scan, or as characteristic asymmetrical cortical hypertrophy of the periosteal and endosteal surface. A low energy traumatic event (i.e. fall from standing height or less) may result in completion of a pre-existing incomplete fracture.

Do stress fracture and insufficiency fractures differ?

The distinctions between stress fracture and insufficiency fracture are not rigorous. There was general agreement that insufficiency fractures occur **with normal activity in abnormal bone**. However, there was a minority opinion that some low trauma fractures (i.e., more force than that found with normal activity) of abnormal bone could be called insufficiency fractures. There was agreement that stress fractures may be caused by **increased activity in normal quality bone** in the absence of external trauma. Moreover, it was recognized that "increased activity" is a relative term. Stress fractures may occur when very sedentary people increase their level of activity to that of the average young or middle-aged adult. **Stress fractures** may occur in normal bone when there is an increase from normal to extremely high levels of activity, for example in the training of military recruits. There was some disagreement about the methods for separating insufficiency fractures from other stress fractures, particularly in older adults. Some consultants suggested that bone must be "fragile" to describe it as an insufficiency fracture (bone fracture without thickening of cortex). Others countered by stating that stress fractures may occur

in relative strong bone if the intensity of activity is sufficiently great. Thus, the pathology is similar.

One consultant commented that the fractures presented by Dr. Lane (and referred to as 'stress' fractures) should be characterized as pathologic fractures because they were complete fractures. By the description of generalized bone thickening, these would not be classified as stress fractures based on radiographic criteria alone.

What are the radiological features of a stress fracture?

Hot spots on bone scan, periosteal apposition, areas of osteolysis, focal thickening and usually only on one cortex, usually on the lateral side. Radiological changes due to stress fractures develop over a period of time. One point made by several consultants was that usually chronic incomplete stress fractures are asymmetric (by cortex) with bone formation only on one cortex, usually on the lateral cortex. The characteristic presentation in the Lane study (ie: subtrochanteric fracture with generalized symmetrical cortical thickening) is not typical of change due to a stress fracture.

What are the typical sites of stress fracture in the lower extremities?

Metatarsals, tibia, pelvis. In older women, sacral and pelvic fractures. In glucocorticoid-induced osteoporosis (GIOP), vertebral and femoral neck stress fractures may occur following aseptic osteonecrosis. Other stress fracture sites in GIOP include ribs.

Is there a difference in the site distribution according to age and gender?

Males - Metatarsal, tibia

Females - Tibia, metatarsals, pelvis.

Sacral and pelvic fractures are more common in the elderly.

What are the risk factors for stress fracture of the femur and other lower extremity bones?

Osteoporosis; radiotherapy; marathon training; dancing at a wedding; small bone diameter; amenorrhea, smoking, Depo-provera, previous inactivity; increased loading on bone. One consultant observed that many femoral shaft stress fracture patients have bowing of the legs; they are usually short in stature and have "big" bones.

What is the case finding definition of the fractures in question?

The radiographic pattern of fractures that appeared to be more frequently observed with bisphosphonate users in the reports from the Hospital for Special Surgery group required that fractures be in the subtrochanteric area (5 cm from the lesser trochanter) or more distal femoral shaft, with a simple transverse fracture path (not oblique or spiral), and cortical "hypertrophy" (the presence of cortical thickening on radiographs was a prominent feature of the fractures described by Lane et al.). The consultants agreed that "thick cortices" was the correct term and "hypertrophy" was incorrect, as there was no evidence that cortices had either enlarged or had a different cortical thickness from that found in younger adults. The HSS group did not find an association between

these fractures and prodromal pain or radiographic evidence of chronic incomplete stress fracture (e.g., focal asymmetrical cortical thickening).

Subtrochanteric fractures include those that are entirely below the level of the lesser trochanter. Some suggested that fractures with as much as 20% of their length above the level of the lesser trochanter could be labeled subtrochanteric, but there was not consensus on this point.

What are the clinical features?

While the majority of patients in the HSS series have not had reported prodromal pain, other case reports reported prodromal pain weeks or months before complete fracture. Consultants cautioned that hip pain is present from time to time in the great majority of elderly people, so care must be taken to investigate whether pain is characteristic of that of a stress fracture in that region and not the much more common pain of rheumatologic disease.

What are the radiographic features?

Dr. Lane reported that approximately 2/3 of patients on alendronate in his observational study had an easily identified X-ray pattern that he described as "simple with thick cortices" pattern. The proportion of patients in his study with "simple transverse fractures" and "thick cortices" appears greater and the proportion with "complex spiral fractures" and "thin cortices" appears smaller in patients treated with bisphosphonates. Several consultants commented that the "simple with thick" fractures seemed to be occurring in what appeared to be non-osteoporotic bone.

Generalized concentric cortical thickening or generalized cortical thickening with an area of reactive periosteum, sometimes bilaterally, was observed in Dr. Lane's series. When the fracture was complete, the fracture line was transverse oblique with a cortical beak on one side. This pattern was different from the spiral fractures, extending up above the lesser trochanter with thin cortices as observed in the majority of the non-bisphosphonate treated patients in Dr. Lane's series.

What type of epidemiology study might be used to better understand whether there is an association of bisphosphonates with low-energy subtrochanteric/femoral shaft fractures and/or altered distribution of femoral fractures?

There are currently no data on the epidemiology of the pattern of subtrochanteric fractures (e.g., simple transverse, oblique or spiral) or the thickness of proximal femoral cortices (thicker or thinner than average) in patients with subtrochanteric fractures. Studies to delineate the epidemiology of subtrochanteric / proximal femoral shaft fractures are required prior to a study of treatment-related risk of these rare fractures. A prospective controlled clinical trial to determine whether there is treatment-related risk would be unlikely to be acceptable to Ethical Committees (due to the need for placebo controlled design), and even without that barrier, would need to be much longer and larger than previous fracture end point studies as fractures in this region of the femur are rare.

The consultants suggested reviewing any large epidemiologic study with long-term follow up that has

evaluated fractures, such as the Study of Osteoporotic Fractures (SOF) that has also gathered data on femoral cortical bone thickness using pelvic radiographs. SOF also has HSA (Hip Structural Analysis of DXA data) and has data on hip and spine BMD to look for concordance (or discordance).

Another study that might yield useful data is an epidemiology study of low energy femoral shaft fractures in skeletally mature patients over a 10 year period (January 1985 to December 1994) in and around Helsinki, Finland. A publication [Salminen et al., Clin Orthop Rel Res 2000; 372: 241–249] from the group of investigators (predating bisphosphonate use) found an incidence of subtrochanteric fracture of 7.8 per 100,000 person-years for people over age 60. The most common fracture pattern was spiral (although there were some transverse and transverse/oblique fractures) and the average age at fracture was 79 years for women and 60 years for men.

It was acknowledged that review of large medical claim databases was not going to address the questions as precise information on the site of fracture is generally absent, and cortical thickness is not usually recorded. Access to actual radiographs was considered essential.

Prospective epidemiological surveys represent a potential way of assessing treatment-associated risk. However, it was noted that such a survey must be population based, control for selection bias based on fracture history and severity of osteoporosis, and medication use (e.g., glucocorticoid use) associated with both stress fractures and bisphosphonate use. Such a survey would also need to include an objective

review of radiographs by a person unaware of the patient's treatment. If these requirements were met, such a survey would need to be very large.

Pathophysiology:

What is the pathophysiology of low energy subtrochanteric/femoral shaft fractures in untreated patients?

Deficient bone quantity (low BMD and osteoporosis) and low bone strength (e.g., Paget's disease of bone, osteogenesis imperfecta, osteopetrosis, glucocorticoid osteoporosis, regional radiotherapy) all increase the risk of subtrochanteric fractures.

Does the pathophysiology differ with regard to bisphosphonate treatment?

It is not known whether treatment with bisphosphonates increases the risk of subtrochanteric fractures. No pathological mechanism has been demonstrated. After reviewing a series of radiographs presented by Dr. Lane, the consultants agreed with Dr. Lane that the distribution of the radiographic appearance of bone and the fracture pattern appeared to be different in bisphosphonate users as compared to non-users. It was pointed out by several consultants that the fracture pattern (simple transverse) was expected in people with thick cortices.

Consultants did not think that bisphosphonates could thicken cortices, rather they could only prevent cortical thinning. The hip structural analysis (HSA) data from FIT/FLEX only reflected an increase in cortical thickness of 3–4% over placebo after 3–4 years of treatment. Moreover, this very small change may be due to the either the effects of increased cortical BMD on the edge detection software used for HSA or

to a decrease in cortical thickness in the placebo group. Also, in a case report by Kwek [Kwek, Goh et al, Injury, Int J. Care Injured 2008, *in press*], serial X-rays of a patient before bisphosphonate therapy, during and then after the fracture appear to show that the patient's cortices were as thick before therapy began.

It was hypothesized that this group may be a subgroup of low turnover osteoporotic women that had been put on therapy, or perhaps patients with low BMD at the spine but normal BMD at the hip. Some proposed the thick cortices could be phenotypic of a low turnover state or some type of heterozygous unidentified bone disease state existing prior to the initiation of BPs. However, no one was aware of a study that investigated the relationship between bone turnover and cortical thickness in the femur of osteoporotic patients.

The importance of collagen to bone strength was also discussed. Collagen ages by accumulation of advanced glycation endproducts and is most responsible for conferring "toughness" to bone. It was opined that if collagen did not get adequately renewed through bone turnover that it would contribute to increased brittleness of bone and decreased strength.

"Oversuppression" of bone turnover was discussed as a potential mechanism of increased bone fragility. There are no data to indicate whether "oversuppression" exists and the consultants recommended against describing the potential mechanism of subtrochanteric/femoral shaft fractures as "oversuppression". Bone remodeling in patients treated with bisphosphonates decreases very early in

treatment and does not progress thereafter. The magnitude of bone turnover reduction correlated with lower non-vertebral fracture risk in FIT and in studies of several other bisphosphonates. It was pointed out that normal, healthy bone turnover on bone biopsies is skewed toward the left (toward low normal turnover). Even if tetracycline double-label is not observed in trabecular bone, it is usually always present in cortical bone and this fracture type is described as a cortical bone fracture. There are no data to indicate that patients with subtrochanteric fracture have a bone turnover rate lower than that seen in the typical bisphosphonate treated patients (without fracture). When biochemical markers of bone turnover were available in case reports, they tended to be within the normal range in these patients. Stress fractures in the patients with subtrochanteric fractures and prodromal symptoms suggestive of incomplete fracture show evidence of increased local bone formation (hot spots), in both bisphosphonate-treated and untreated patients.

There was consensus that "if" decreased bone turnover were associated with stress fracture risk it would be similar for all bisphosphonates (at doses used to treat osteoporosis), as well as other drugs (e.g., estrogen in the menopause, or RANK-L inhibitors) that inhibit osteoclast activity, although at this time evidence for an increase in subtrochanteric fractures and use of inhibitors of bone resorption has not been demonstrated.

The consultants wanted to develop some standard of care based on what we know now, i.e. if the patient has symptoms of prodromal pain suggestive of incomplete stress fracture, a femoral shaft X-ray should be taken

to rule out stress fracture. If there is evidence of a stress fracture on one side, an X-ray should also be taken on the opposite side. If the X-ray is not definitive, a bone scan should be done and the current standard of care for identified stress fractures should be followed.

Many of the consultants thought that they would consider stopping bisphosphonates in the setting of a stress fracture of the subtrochanteric / shaft regions of the femur. All acknowledged that there are no data to indicate that the fracture would heal more quickly and that fractures at more common sites of osteoporotic fracture may be more likely if treatment were discontinued. It was also acknowledged that although remodeling is delayed, there is no data to suggest impaired fracture healing in bisphosphonate treated patients. Most agreed that they would consider interruption of treatment in the setting of an incomplete stress fracture (documented by a positive bone scan or radiograph) as well, albeit no data supporting this practice is available either. There was consensus that the current state of knowledge regarding clinical management was extremely limited.

At the close of the meeting, Dr. Lane acknowledged that his data did not establish that bisphosphonates increase the risk for these types of fractures over their background rate of occurrence, and that he understood that his data was only hypothesis generating.

[Exhibit 122 to Ecklund Declaration]

James Adams
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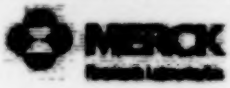
September 15, 2008



Mary Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Annendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 20-560: FOSAMAX™ Tablets
(Alendronate Sodium)

Prior Approval Supplement

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act, we submit, for the Agency's review and approval, a supplement to NDA 20-560.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the Labeling Section of the approved New Drug Application for FOSAMAX.

Merck is proposing to add language to both the Precaution and Adverse Reaction/ Post-Marketing Experience section of the label to describe low-energy fractures that have been reported, of which some have been stress/ insufficiency, at the subtrochanteric region of the femoral shaft. While these fractures are less common than other osteoporotic low-energy fractures, they occur in a familiar population of elderly individuals and have been reported prior to the availability of bisphosphonates. It is not possible with the present data to establish whether treatment with alendronate increases the risk of low-energy subtrochanteric and/or proximal femoral shaft fractures. Nevertheless, considering the clinical importance of these fractures in patients with osteoporosis and their temporal association with bisphosphonate use, the Company believes that it is important to include an appropriate statement about them in the product label. This may further increase physicians' awareness of possible fractures in some osteoporotic patients at risk and all ow early intervention, thereby possibly preventing the progression to complete fracture and/or other complications.

As per FDA Guidance to Industry: *Providing Regulatory Submissions in Electronic Format – Content of Labeling*, the proposed labeling is provided in SPL format. Content of labeling [(201.100(d)(3)] has been included in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

The Microsoft WORD version of the proposed labeling text is also supplied as PROPOSED.DOC within Section 1.14.1.3 Draft labeling text.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

In accordance with the Prescription Drug User Fee Act of 1992 (PDUFA) and reauthorized in the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the Prescription Drug User Fee Amendments of 2002 (PDUFA III), as indicated in the attached Form 3397, no user fee is required for this supplemental application.

We consider the filing of this supplemental New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its content, nor any further communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to James Adams, (732-594-2552) or, in his absence, to Charlotte B. Merritt (732-594-4060).

Sincerely
s/ James Adams
James Adams

Associate Director
Worldwide Regulatory Affairs

* * *

CURRENT CIRCULAR SHOWING REVISIONS

FOSAMAX®
(alendronate sodium) Tablets and Oral Solution

women. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups.

Dental

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., pre-existing dental disease, anemia, coagulopathy, infection).

Patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy should receive care by an oral surgeon. Dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Low-Energy Femoral Shaft Fracture

Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma.[1] Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates.[2] Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care.[3] Interruption of bisphosphonate therapy in patients with stress fractures [4] should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.[3]

Renal insufficiency

FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <34 mL/min). (See DOSAGE AND ADMINISTRATION.)

COMMENTS/SUPPORT

1. [Sec. 2.5: p. 5]
2. [Sec. 2.5: p. 7]
3. [Sec. 2.5: p. 5]
4. [Sec. 2.5: p. 8]

* * *

CURRENT CIRCULAR SHOWING REVISIONS

FOSAMAX®
(alendronate sodium) Tablets and Oral Solution

In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of FOSAMAX 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration. These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with an acute-phase response that has been reported in patients receiving bisphosphonates, including FOSAMAX. See ADVERSE REACTIONS, *Post-Marketing Experience, Body as a Whole.*

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3%

of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 nM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

Body as a Whole: hypersensitivity reactions including urticarial and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with FOSAMAX, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, *Information for Patients*, and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see PRECAUTIONS, *Dental*).

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, *Musculoskeletal Pain*); joint swelling; low-energy femoral shaft fracture (see PRECAUTIONS, *Low-Energy Femoral Shaft Fracture*).

Nervous system: dizziness and vertigo.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveltis, scleritis or episcleritis.

COMMENTS/SUPPORT

Addition of Post-Marketing Adverse Reaction, "low-energy femoral shaft fracture," based on the WAES reports listed on pages 37, 38.

* * *

[Exhibit 124 to Ecklund Declaration]

FDA Media Call
Possible increased risk of thigh bone fracture with bisphosphonates
Moderator: Karen Riley
October 13, 2010

Coordinator: Welcome and thank you for standing by. All participants are in a listen-only mode. During the question and answer portion of today's call, please press star 1 if you would like to ask a question. Today's call is being recorded. If you have any objections, please disconnect at this time. I'll now turn the meeting over to Ms. Karen Riley. Thank you. You may begin.

Karen Riley: Thank you operator. Thank you very much. Welcome ladies and gentlemen. My name is Karen Riley from the FDA's Office of Public Affairs. This is an FDA Teleconference for credential media to discuss safety warnings about bisphosphonates.

By now you should have received an email copy of the FDA press release on this subject or reviewed the press release on the FDA Web site. I also suggest that you take a look at the drug safety communication. You'll

find a link to that document at the bottom of the press release.

Before we take your questions, Rear Admiral Sandra Kweder will make some opening remarks. Dr. Kweder is Deputy Director of the Office of New Drugs in FDA's Center for Drug Evaluation and Research better known by its acronym, CDER. Dr. Kweder.

Sandra Kweder: Thank you Karen and thank you all for joining us this afternoon. I want to reiterate Karen's urging to take a look at our drug safety communication on our Web site where you'll probably find more detailed information.

Today FDA is warning patients and their healthcare providers again about the possible risk of an uncommon form of fracture in patients who take a class of drug known as bisphosphonates to treat or prevent osteoporosis. As you probably know, osteoporosis is a progressive thinning of bone tissue and a loss of bone density. It is most common in women who have gone through menopause.

Over time osteoporosis can put people at risk of fractures that result in pain, hospitalization and surgery. The fractures are usually in the hip

or the spine or the wrist. Patients take bisphosphonates and other medicines to inhibit or slow this loss of bone mass and prevent fractures.

Studies of these drugs which typically last from three to five years have shown that these drugs do reduce the rate of osteoporotic fractures but no treatment has ever been shown to eliminate the risk completely.

What FDA is warning about today is the risk of an uncommon or atypical type of fracture in the thigh bone. Subtrochanteric femur, or thigh bone, fractures are known to occur in patients with osteoporosis. Always have been. However in recent years there has been an increasing number of reports of femur fractures with some unusual features in patients taking bisphosphonates. And one of the things that's unusual about them is they are often associated with very little or no trauma at all.

In 2008 FDA — because of reports of these types of fractures, FDA asked the bisphosphonate manufacturers to provide us with all of the information they had on cases of these types of unusual or atypical fractures from their clinical trials of the drugs.

In March of this year we issued a safety communication about our ongoing review of those data. We found that these fractures were very rare in clinical trials. Patients taking bisphosphonates in the clinical trials were not more likely to have such fractures than patients taking placebo. And epidemiology studies that we had reviewed also did not suggest that the atypical fractures were clearly caused by bisphosphonates.

Recently FDA reviewed a new report by the American Society of Bone and Mineral Research which helped to clarify the features of atypical femur fractures in patients with osteoporosis both with relation to X-ray findings and some clinical characteristics of the patients.

Based on this report we've been able to better assess some of the cases reported to us through our post-marketing adverse event reporting system and hopefully we'll be able to do that also for medical literature reports.

The American Society for Bone and Mineral Research report also provides more information that more closely associates these atypical fractures with long-term

bisphosphonate use. What's important to know about these atypical fractures is that the patients who experience them have fractures — can have a fracture occurring anywhere in the femur shaft which is the long bone of the thigh.

In addition to being less likely to be associated with trauma, patients taking bisphosphonates who experience an atypical fracture are generally younger than patients with typical osteoporotic fractures. In some cases the patients have bilateral fractures of both femurs. And importantly many of these patients describe a dull aching thigh or groin pain that begins weeks to months before a complete fracture occurs.

Now we don't know what the optimal length of time is for patients, particularly post-menopausal women, for taking a bisphosphonate. But in looking at the data the atypical fractures of concern have occurred predominantly in patients who have taken bisphosphonates for five years or more.

In response to these reports, FDA today requested a labeling change in the warnings and precautions section of all bisphosphonate products that

are used to prevent and treat osteoporosis. FDA is also requiring that these products come with a medication guide to better inform patients of the possible risk. This is important because having informed patients may be able to prevent the occurrence of these rare but debilitating fractures. And I want to emphasize that they are quite rare.

I also want to make it clear that our announcement today is an update and should not cause patients taking bisphosphonates to be fearful of their medicine. Bisphosphonates are an important mainstay of osteoporosis management and they have prevented innumerable fractures in their years of use but patients should be informed.

We at FDA will continue to evaluate data about the safety and effectiveness of bisphosphonates when used over a long period of time to prevent and treat osteoporosis.

In the interim, FDA recommends that healthcare professionals be aware of the possible risk of fracture in patients taking bisphosphonates and consider periodic reevaluation of the need for continued therapy once patients have been taking the drug for five or more years.

Certainly any patient on these medicines who develop unexplained thigh or groin pain should be evaluated for the risk of these unusual fractures. For patients who take bisphosphonates for osteoporosis management, we urge them that they should not stop using their medication unless advised to do so by their healthcare professional. They should also report any new thigh or groin pain and be evaluated for a possible risk of femur fracture.

To put this in context, in the United States in 2009 there were over 5 million patients who filled prescriptions for bisphosphonates, most of them women and most of them over the age of 55. And these — the drugs that we are describing in relation to — have an association with these possible fractures are drugs such as Fosamax, Actonel, Boniva and Reclast.

And I'll stop there and we'll take your questions.

Karen Riley: Thank you Dr. Kweder. Again, this is Karen Riley in the press office. And before we take questions, I want to point out that we've also posted on our Web site the letters on bisphosphonates that we sent to the manufacturers. And those can be

accessed by looking — by scrolling down the page where we have posted the drug safety communication and you can find the links to those in that spot.

And I want to remind reporters that when asking a question, please state your name and affiliation and it goes without saying that the questions are to be asked by report credential media only. Please limit yourself to one question and one follow-up so we can get to as many questions as possible.

Operator, we'll take the first question. Thank you.

Coordinator: If you would like to ask a question, please press star 1. Again, that is star 1 to ask a question. The first question comes from Donna Young. Your line is open.

Donna Young: Hello. Thanks for taking my call. I appreciate it. I just had a question as far as like you had said Dr. Kweder that taking bisphosphonates has prevented innumerous or innumerable fractures. Where — kind of what do you base that on? And then also last March when this came up, the agency sort of downplayed the studies that were showing this. So what new data

between March and now have you reviewed?

Sandra Kweder: Okay. Well that's two questions. And I can say that we know that from clinical trials of thousands of patients and these drugs, placebo controlled trials, that they prevent the common osteoporosis-related fractures. The fractures that we're talking about today are really unusual and rare.

I would say from the data from the National Hospital Discharge Survey showed that per 100,000 patients in 1996, this is the year after Alendronate was first approved, there were — in 2006 there were 598 fracture per 100,000 patients hip — I can't even say this — why don't I stop with the numbers. Let's just suffice it to say — because there are lots of sources of data and if we need to get more specific we can come back to that.

Donna Young: Okay.

Sandra Kweder: But the studies that have been done, epidemiology studies showing the benefits of these drugs have over and over and over again demonstrated that they do prevent fractures.

With regard to what has changed since March, several things. And I would say the most — the data that

we were able to review up until March was from the clinical trials as well as from some case reports in the literature. There were also some epidemiology studies that really didn't show very much in the way — that really helped us tease out the association between these drugs and these rare atypical fractures.

However, the report by — that recently was put out by the American Society for Bone and Mineral Research using some Kaiser data have really helped us understand these fractures a little bit better and make us confident that this is something that is potentially more closely related to these drugs, particularly long-term use than we previously had evidence for.

There were certainly — when you read the individual reports or as we have met with patients who have experienced these rare fractures, their cases are quite striking but trying to sort that out from clinical trial data and other things in the literature was hard. The report by the American Society of Bone and Mineral Research has really been helpful to us in better understanding this. Does that answer your question?

Donna Young: Yes. Thank you.

Karen Riley: Thank you. And before we go on I was remiss in not also introducing Dr. Theresa Kehoe who's the team leader in the Division of Reproductive and Urologic Products in CDER's Office of Drug Evaluation 3 who will also be able to chime in and answer any questions if need be.

So let's go on to the next — oh, and I'll spell her name. It's Theresa with a T-H, T-H-E-R-E-S-A and then Kehoe is K-E-H-O-E. So okay, let's go to the next question please.

Coordinator: And we have a question from Jennifer Corbett. You're line is open.

Jennifer Corbett: Yeah. Hi. Thanks for taking my question. The question I had again was just trying to put this in context. Dr. Kweder mentioned that there is — you said there were about 5 million prescriptions filled last year and the American Society for Bone and Mineral Research, their task force looked at 310 fractures. Do you guys — I mean is that about the universe that you think we're looking at, the 310 figure? Or do you have different information or additional reports of these atypical fractures?

Theresa Kehoe: This is Theresa Kehoe. I think our numbers are similar to what the ASBMR has looked at. But obviously

notorious with the AERS reporting system is the underreporting rate. So we suspect that there is a lack of awareness among both patients and physicians that these type of fractures may be associated with the actual drugs that they're taking to prevent fractures.

Jennifer Corbett: Right.

Theresa Kehoe: But so we are aware of that and that's one of the reasons to go ahead and get this message out.

Jennifer Corbett: Okay. Thank you.

Karen Riley: Thank you. Next question please. The next question is from Cheryl Thompson from the American Journal of Health-System Pharmacy. Your line is open.

Cheryl Thompson: Hi. Thank you. Does the addition of a medication guide mean that these drugs have a Risk Evaluation and Mitigation Strategy formally?

Sandra Kweder: Yes, actually it does. It does mean that. The existence of a medication guide does formally fall under the rubric of a REMS. And for those that aren't aware, a medication guide is an information pamphlet or an information sheet that must be given to the patient every time a prescription is dispensed.

Cheryl Thompson: Okay. Thank you. And a follow-up. Are there any other components of this REMS?

Sandra Kweder: No, there are not.

Cheryl Thompson: Thank you.

Karen Riley: And that was Dr. Kweder answering that question. Next question please.

Coordinator: Comes from Lisa Richwine from Reuters. Your line is open.

Lisa Richwine: Hi. Thanks for taking my question. In the earlier FDA communications I seem to recall there is — it singled out oral drugs as having this risk but the warning is going to apply to the injectable drugs as well. Have you seen cases with both the oral and the injectable drugs?

Sandra Kweder: Yes, we have. We certainly have more reports associated with the oral drugs but they are also much more commonly prescribed. But we do have — we have had reports from all of them.

Lisa Richwine: Okay. And if I could get a follow-up question. Can you give us an exact number? You said the cases you had were similar to the 310 or so reported by the Bone and Mineral Research Group and can you give us your exact number?

Sandra Kweder: Yeah. Actually we probably — we can't give you an exact number. One

of the things that — one of the main reasons is that the reports are often quite incomplete. And based on the definition of, you know, what constitutes absolutely an atypical fracture that the American Society of Bone and Mineral Research has put forward, a lot of that information is missing in the reports that we have so we need to go back and reevaluate those to see how many we actually have.

I think that going forward now that that standard case definition is out in the public domain, the information that we get in these reports will be much better and we'll be able to have a more accurate accounting of how often these occur and learn even more about their characteristics.

Lisa Richwine: Okay. Thanks.

Karen Riley: And that was Dr. Kweder. Thank you. Next question please.

Coordinator: Your next question comes from Martin Gorvine from Pink Sheet. Your line is open.

Martin Gorvine: Yes. Hello. Thanks for taking my question. Do the labeling changes — it was mentioned those are going into warnings and precautions, are they going to also be in a boxed warning section for these drugs?

Theresa Kehoe: This is Theresa Kehoe. No, it will not be a boxed warning. This will be in the warnings and precautions section.

Martin Gorvine: All right. Thank you.

Karen Riley: Thank you. Next question please.

Coordinator: Your next question comes from Deborah Kotz from U.S. News and World Report. Your line is open.

Deborah Kotz: Hi there. Thanks for taking my question. I'm wondering about one of the lines in the press release that says that — recommending that health professionals be aware of the risks and evaluating patients who are on bisphosphonates for longer than five years and in terms of the larger topic of whether bisphosphonates are safe to take beyond five years. What exactly should patients ask their physicians to do? What should they — how should they be evaluating them to determine whether they should stay on these drugs?

Theresa Kehoe: I think in many cases when we look at the case reports, what we are seeing is that patients are on bisphosphonates and they actually normalize or close to normalize their bone density and they remain on the bisphosphonates. So this may be a case where if because

bisphosphonates are retained in the bone for such a long period of time where if the bone mineral density is significantly improved that a patient may be able to come off the bisphosphonate for it could be years, it could be a shorter time.

But what I can tell you is that we are very actively evaluating this issue and we are not necessarily ready to make recommendations as far as the duration of treatment, whether drug holidays versus stopping the drug. We are still looking at all of those issues.

Sandra Kweder: That was Theresa Kehoe and this is Sandy Kweder. I'm going to add to that. I think that any — you know, when patients and physicians should be having conversations about just like any medicine. Do I still need this medicine? Is this still the best medicine for me? And the answer to that will depend on what else is happening.

Maybe other medications that they started taking that maybe may be substitutes or just as good as a bisphosphonate. Or in particular related to as we're warning today, if the patient has been experiencing any kind of unexplained pain of the groin or thigh. Making sure that

they have a conversation with their physician about any symptom like that is extremely important to govern what kind of management is appropriate.

I hope that answer — those help you.

Deborah Kotz: Yes. Thanks. And just one follow-up. Do you have a percentage of how many patients had this unexplained pain in their groin or thigh before they had the fracture?

Theresa Kehoe: In the case reports that we have it's over 50%. So it is the majority of patients.

Sandra Kweder: And again, that often occurs weeks to months — begins weeks to months before the actual fracture.

Karen Riley: Thank you. Next question please.

Coordinator: Your next question comes from Robert Lowes from Medscape Medical News. Your line is open.

Robert Lowes: Hi. Thank you for taking my call. I wanted to ask for some clarification about this dull aching thigh or groin pain that precedes the complete fracture. Looking at your data summary, you're summarizing what the American Society for Bone and Mineral Research says, what its task force reported. They — it says here, "Many patients report this pain

weeks to months before a complete fracture occurs."

So I'm wondering what does that pain actually signify? Does it signify the beginnings of a fracture or does it signify something else that's related to the fracture? And if a person recognizes this pain, what can possibly be done for that patient in terms of dealing with an impending total fracture? Is there anything a patient can do or any treatment they can receive that might avert this complete snap so to speak?

Theresa Kehoe: Well I think that the American Society for Bone and Mineral Research does bring out the thigh pain in their report. But we have also gone back to the reports that we have received and again have found that over 50% of patients are having — are also in the reports we have had the thigh and groin pain.

As far as treatments, what we have right now is we do not have any clinical studies to say that one treatment is better than the other. Certainly as outlined in the American Society for Bone and Mineral Research they recommend stopping the drug. Sometimes patients can be treated conservatively with non-weight

bearing and be able to avert a complete fracture. And sometimes if the pain continues, they may need orthopedic care.

So I think a lot of this will depend on the patient and the physician and what exactly the history is and what the patient's symptoms are.

Robert Lowes: But is the — to follow up, is the pain the result of a partial fracture or is it related to something else?

Theresa Kehoe: It appears that it might be related to an actual partial fracture such as a stress fracture.

Sandra Kweder: The problem is that we don't know because the descriptions of pain having been there usually come, you know, are something that's reported in retrospect. There aren't studies or really much in the literature that follows these patients prospectively to understand the evolution of the pain and what the pathology is that is paralleling it.

Robert Lowes: Okay. Thank you very much.

Karen Riley: And by non-weight bearing, you mean don't stand on your leg or something?

Sandra Kweder: Yeah.

Karen Riley: Okay. Very good. Operator, do we have any more people on the line?

Maybe we have time for two more questions.

Coordinator: Yes. We have one person. And again if you'd like to ask a question, please press star 1. Star 1 to ask a question please. And next is Matt Perrone. Your line is open.

Matt Perrone: Hi guys. Can you talk about the typical duration that people stay on these drugs? You said this was more common in people who have been taking bisphosphonates for five years. But is that rare or is that pretty typical?

Theresa Kehoe: We don't really have any data to tell us exactly how long patients remain on bisphosphonates. We — in the reports that we have seen there are some patients that have been on bisphosphonates for 10 to 15 years. Certainly I think there's probably a spectrum.

Matt Perrone: Okay. And can you talk at all about how these drugs typically are supposed to work, how they typically strengthen bones and how that could in rare cases lead to these type of fractures?

Theresa Kehoe: The drugs, the bisphosphonates work by inhibiting the osteoblast which is the cell that resorbs bone, that lessens bone. How — but exactly how the method for what the

association is, there are many postulates of what could possibly be the mechanisms that bisphosphonates cause these types of fractures. What I would recommend, I think the American Society for Bone and Mineral Research does a very nice job of looking at what all of the possible mechanisms are.

Matt Perrone: And how is the FDA going to determine which of those is the culprit here?

Sandra Kweder: I think this is an area of intense research. This is Sandy Kweder. This is in the area of intense research in the bone and mineral community. You know, the whole not only related to these fractures but related to what optimal therapies are in general to prevent or treat osteoporosis. So we will be following that very closely as we do — related not just to these drugs but in looking at all kinds of treatments for osteoporosis.

Karen Riley: Thank you Matt. We did have — I did get an email from one of the reporters on the call who did ask for a little bit more information on the numbers of fractures prevented and we do have some information on that. Dr. Kehoe will explain.

Theresa Kehoe: Sure. I think probably the best data out there is the study looking at the

National Hospital Discharge Survey which looks at discharge rates per 100,000 persons for hip fractures. And obviously hip fractures are one of the more problematic fractures in the osteoporotic population.

If you recall Alendronate was the first bisphosphonate approved for osteoporosis in 1995 and all of the other ones have been subsequent to that. In 1996 when we look at the National Hospital Discharge Survey, the rate of hip fracture discharges was 598 per 100,000 persons. In 2006, so after approximately ten years of bisphosphonates being on the market for treating osteoporosis, the hip fracture discharge rate had fallen to 428 per 100,000 persons. So that is a pretty substantial decrease in hip fracture rates over that ten-year period due to osteoporosis therapies, mostly the bisphosphonates.

Karen Riley: Thank you. Thank you. That was Dr. Theresa Kehoe. And again for those of you who didn't catch the spelling of her name, her last name is spelled K-E-H-O-E and her first name Theresa, T-H-E-R-E-S-A. And she is a team leader in the Division of Reproductive and Urologic Products in CDER's Office of Drug Evaluation 3.

Okay. This concludes today's media teleconference. Thank you for your participation. A replay will be available in about an hour. If you have any follow-up questions, please don't hesitate to call me, Karen Riley, at 301-796- 4674 or even better email me at karen.riley, that's R-I-L-E-Y, @fda.hhs, as in Sam, dot gov. Thank you.

Coordinator: Thank you. This concludes today's call. You may disconnect at this time.

END

[Exhibit 148 to Ecklund Declaration]

To:	Adams, James H (WRG) <james_adams@merck.com>
From:	Stiller, Karl <Karl.Stiller@fda.hhs.gov>
Cc:	
Bcc:	
Received Date:	2009-04-15 19:51:43
Subject:	Tcon for Fosamax products

There seems to be some confusion regarding the discussion last week. What Dr. Monroe and Dr. Kehoe proposed to Charlotte Merrick was that the currently pending SLRs (20-560 s052; 21-575 s013; 21-762 s006) for atypical fracture could be approved at this time only for inclusion of the atypical fracture language proposed in the postmarketing adverse events section of the label. If Merck agrees to hold off on the W&P language at this time, then we can go ahead and close out these supplements.

We would then work with OSE and Merck to decide on language for a W&P atypical fracture language, if it is warranted. We also let Merck know that we are working with our dental colleagues on acceptable ONJ language and once we have that, we will work with Merck on the ONJ language.

What Dr. Kehoe proposed was that she was hopeful that an agreement could be reached with Merck regarding the language for ONJ and possibly atypical fracture in time to allow that language to be included in the PLR conversion supplement.

At this time, we are not able to commit to doing a "quick" review of a new SLR supplement. However, if Merck is accepting the language from the esophageal SRL, that may be able to be included - we would be able to approve that with the atypical fracture postmarketing language.

I have reserved 3:30 pm - 4:00 pm for a Tcon to discuss the matter, if necessary.

Call in number: 1-888-397-4120
Pass code: 8088980

LCDR Karl Stiller, R.Ph.
Regulatory Health Project Manager
Division of Urologic and Reproductive Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
301-796-1993

[Exhibit 149 to Ecklund Declaration]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

NDA 20-560/S-054, NDA 21-575/S-015,
NDA 21-762/S-008

COMPLETE RESPONSE

James H. Adams
May 22, 2009

Merck & Co., Inc.
Attention: James Adams, M.S.
Associate Director, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065-0900

Dear Mr. Adams

Please refer to your supplemental new drug applications (sNDAs) dated September 15, 2008, received September 15, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

FOSAMAX (alendronate sodium) Tablets
(NDA 20-560/S-054)
FOSAMAX (alendronate sodium) Oral Solution
(NDA 21-575/S-015)

FOSAMAX Plus D
(alendronate sodium/cholecalciferol) Tablets
(NDA 21-762/S-008)

We acknowledge receipt of your amendments for FOSAMAX Tablets and FOSAMAX Oral Solution, both dated September 19, 2008.

These supplemental new drug applications propose adding language to the **PRECAUTIONS** section and the **ADVERSE REACTIONS, Post-Marketing Experience** subsection of the Package Inserts (PIs) to describe low-energy fractures at the subtrochanteric region of the femoral shaft. In addition these supplements propose adding language describing this type of fracture in the Patient Package Inserts (PPIs).

We have completed the review of your applications, as amended, and have determined we cannot approve these applications in their present form. We have described below our reasons for this action and our recommendation to address this issue.

1. While the Division agrees that atypical and subtrochanteric fractures should be added to the **ADVERSE REACTIONS, Post-Marketing Experience** subsections of the FOSAMAX Tablets and Oral Solution and FOSAMAX Plus D Tablets labels, your justification for the proposed **PRECAUTIONS** section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported

by the available literature and post-marketing adverse event reporting.

2. We recommend that you add "low energy femoral shaft and subtrochanteric fractures" in the **ADVERSE REACTIONS, Post-Marketing Experience** subsection of the respective package inserts.

Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/datacouncil_spl/html.

When responding to this letter, submit labeling that includes all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with this change before approval of these supplemental applications.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

Scott Monroe, M.D.
Director
Division of Reproductive and
Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation
and Research

/s/ Scott Monroe
5/22/2009 11:06:15 AM

[Exhibit 150 to Ecklund Declaration]

To: **Adams, James H (WRG) <james_adams@merck.com>; Santora, Arthur C. <art_santora@merck.com>; Miteva, Yanna R <yanna_miteva@merck.com>; Hampton, Tonja W <tonja_hampton@merck.com>; Holston, James <james_holston@merck.com>; Hutnyan, John J. <john_hutnyan@merck .com>; Frank, Lori J. <lori_frank@merck.com>; Birzin, Elizabeth T. <ellzabeth_birzin@merck.com>; Stebbins, Enid <enid_stebbins@merck.com>; Thornton, Rosemary A <rosemary _thornton@ merck.com>**

From: **Reiss, Theodore F. </O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=REISST>**

Cc: **Bold, Thomas M. <thomas_bold@merck.com>; Merritt, Charlotte B. <charlotte_merritt@merck.com>; Kloss, Michelle W. <michelle_kloss@merck.com>; King, Vicki M <vicki_king2@ merck.com>**

Bcc:

Received Date: 2009-05-22 21:58:57

Subject: RE: FDA letter regarding low energy femoral shaft fractures

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What are the next steps?

From: Adams, James H (WAG)
Sent: Friday, May 22, 2009 12:41 PM
To: Reiss, Theodore F.; Santora, Arthur C.; Miteva, Yanna R; Hampton, Tonja W; Holston, James; Hutnyan, John J.; Frank, Lori J.; Birzin, Elizabeth T.; Stebbins, Enid; Thornton, Rosemary A
Cc: Bold, Thomas M.; Merritt, Charlotte B.; Reiss, Theodore F.; Kloss, Michelle W.; King, Vicki M
Subject: FDA letter regarding low energy femoral shaft fractures

Dear all,

Please find attach a fax from the FDA not approving our PAS re. low-energy femoral shaft fractures << File: Document.pdf >>. The Division agrees that a description of these fractures should be added to the Adverse Reactions, Post-Marketing section of the label. However, it believed that our justification to support the proposed Precaution text was inadequate. It believes that "stress fractures" may not be clearly related to atypical subtrochanteric fractures. Furthermore, the Division to not agree with the inclusion of risk factors for stress fractures.

Please note that the Division has requested that the following text be added to the Post-marketing section- "low energy femoral shaft and subtrochanteric fractures"

Diane,

Please add fax to e-dossier. Thanks.

Jim

[Exhibit 151 to Ecklund Declaration]

To: **Adams, James H (WRG) <james_adams@merck.com>**

From: **Santora, Arthur C. </O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=SANTORAA>**

Cc:

Bcc:

Received **Date: 2009-05-22 21:18:16**

Subject: **RE: FDA letter regarding low energy femoral shaft fractures**

Thanks, Jim. Timely FAX.

Kind of ironic that the TGA wouldn't let us mention low energy fractures in general and the FDA wouldn't let us mention stress fractures.

Art

From: Adams, James H (WAG)

Sent: Friday, May 22, 2009 12:41 PM

To: Reiss, Theodore F.; Santora, Arthur C.; Miteva, Yanna R; Hampton, Tonja W; Holston, James; Hutnyan, John J.; Frank, Lori J.; Birzin, Elizabeth T.; Stebbins, Enid; Thornton, Rosemary A

Cc: Bold, Thomas M.; Merritt, Charlotte B.; Reiss, Theodore F.; Kloss, Michelle W.; King, Vicki M

Subject: FDA letter regarding low energy femoral shaft fractures

Dear all,

Please find attach a fax from the FDA not approving our PAS re. low-energy femoral shaft fractures << File: Document.pdf >> . The Division agrees that a description of these fractures should be added to the Adverse Reactions, Post-Marketing section of the label. However, it believed that our justification to support the proposed Precaution text was inadequate. It believes that "stress fractures" may not be clearly related to atypical subtrochanteric fractures. Furthermore, the Division to not agree with the inclusion of risk factors for stress fractures.

Please note that the Division has requested that the following text be added to the Post-marketing section- "low energy femoral shaft and subtrochanteric fractures"

Diane,

Please add fax to e-dossier. Thanks.

Jim

[Exhibit 156 to Ecklund Declaration]

FDA **U.S. Food and Drug Administration**

Protecting and Promoting Your Health

Drugs

FDA Drug Safety Communication: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures

The FDA has issued new information about this safety issue, see the FDA Drug Safety Communication issued 10-13-2010[1].

Safety Announcement

[03-10-2010] Patients and healthcare professionals may have questions about oral bisphosphonate medications and atypical subtrochanteric femur fractures – fractures in the bone just below the hip joint. Oral bisphosphonates are commonly prescribed to prevent or treat osteoporosis in postmenopausal women. Common brand names of medications in this class include Fosamax, Actonel, Boniva, and Reclast.

Recent news reports have raised the question about whether there is an increased risk of this type of fracture in patients with osteoporosis using these medications. At this point, the data that FDA has reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures. FDA is working closely with outside experts, including members of the

recently convened American Society of Bone and Mineral Research Subtrochanteric Femoral Fracture Task Force, to gather additional information that may provide more insight into this issue.

Based on published case reports of atypical subtrochanteric femur fractures occurring in women with osteoporosis using bisphosphonates, FDA, in June 2008, requested information from all bisphosphonate drug manufacturers regarding this potential safety signal. All available case reports and clinical trial data were requested. FDA's review of these data did not show an increase in this risk in women using these medications.

In addition, FDA reviewed a December 2008 article in the Journal of Bone and Mineral Research by *Abrahamsen* et al[1], that analyzed data from two large observational studies in patients with osteoporosis. The authors concluded that atypical subtrochanteric femur fractures had many similar features in common with classical osteoporotic hip fractures, including patient age, gender, and trauma mechanism. The data showed that patients taking bisphosphonates and those not taking bisphosphonates had similar numbers of atypical subtrochanteric femur fractures relative to classical osteoporotic hip fractures.

This communication is in keeping with FDA's commitment to inform the public about its ongoing safety review of drugs. The agency will continue to review new information as it becomes available and will update the public once the agency's review is complete.

Healthcare professionals should continue to follow the recommendations in the drug label when

prescribing oral bisphosphonates. **Patients** should not stop taking their medication unless told to do so by their healthcare professional. Patients should talk to their healthcare professional about any concerns they have with these medications.

Additional Information for Patients

If you currently take an oral bisphosphonate you should:

- Not stop taking your medication unless told to do so by your healthcare professional.
- Talk to your healthcare professional if you develop new hip or thigh pain or have any concerns with your medications.
- Report any side effects with your bisphosphonate medication to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals should:

- Be aware of the possible risk of atypical subtrochanteric femur fractures in patients taking oral bisphosphonates.
- Continue to follow the recommendations in the drug label when prescribing oral bisphosphonates.
- Discuss with patients the known benefits and potential risks with using oral bisphosphonates.
- Report any adverse events with the use of oral bisphosphonates to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

References:

1. Abrahamsen B., Eiken P., Eastell R. Subtrochanteric and Diaphyseal Femur Fractures in Patients Treated With Alendronate: A Register-Based National Cohort Study. *J Bone Miner Res.* 2009 Jun;24(6):1095–102.

Related Information

- Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa) Information[2]
- Podcast for Healthcare Professionals: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures[3] 3/17/2010
- FDA Drug Safety Communication: Safety update for osteoporosis drugs, bisphosphonates, and atypical fractures[4] 10/13/2010

Contact FDA

1-800-332-1088
1-800-FDA-0178 Fax
Report a Serious Problem

MedWatch Online[5]

Regular Mail: Use postage-paid FDA Form 3500[6]

Mail to: MedWatch 5600 Fishers Lane Rockville, MD 20857

Page Last Updated: 07/18/2011

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Email FDA

[Exhibit 159 to Ecklund Declaration]

FDA U.S. Food and Drug Administration

Protecting and Promoting Your Health

Drugs

FDA Statement on ASBMR report: Possible Increased Risk of Certain Types of Thigh Bone Fractures with Long-Term Bisphosphonates Use

[9/14/2010] FDA appreciates the report from the American Society of Bone and Mineral Research's (ASBMR's) expert Task Force, released today, providing important perspectives on the potential association between long term treatment with the class of osteoporosis drugs known as bisphosphonates and a rare but serious type of fracture of the thigh bone (femur). The report includes a case definition that describes the atypical features of these unusual femur fractures. FDA believes this case definition will help greatly in identifying cases and reporting on them, and should facilitate future studies comparing the frequency of these unusual fractures both in patients treated with bisphosphonates and those who have not received bisphosphonates.

Bisphosphonates have long been effective in reducing common bone fractures in individuals with osteoporosis. Although it is not clear if bisphosphonates are the cause, these unusual femur fractures have been identified in patients taking these drugs. FDA recommends that healthcare

professionals be aware of the possible risk of unusual femur fractures in patients taking bisphosphonates. Patients should talk to their healthcare professional if they develop new thigh or groin pain so that they may be evaluated to rule out a femur fracture. Patients should not stop taking their medication unless told to do so by their healthcare professional. Patients and healthcare professionals should report any side effects with the use of bisphosphonates to FDA's MedWatch program.

The optimal duration of bisphosphonate treatment for osteoporosis is unknown. Clinical trial data for bisphosphonates approved for the prevention and/or treatment of osteoporosis support effectiveness for the reduction of common bone fractures for three to five years.

Since the initial report of unusual fractures with bisphosphonates was published, FDA has been diligently monitoring this issue. We have been reviewing all the scientific data available regarding their safety and effectiveness when used for more than three to five years for the treatment and prevention of osteoporosis. We have talked with patient groups and have requested clinical trial data from the manufacturers of bisphosphonate products as part of this ongoing safety review.

The ASBMR Task Force's recommendations include recommended changes to product labels alerting healthcare professionals and patients to the possibility of unusual femur fractures with long-term use of bisphosphonates. FDA has assembled and is thoroughly reviewing all long term data available on the products, as well as all safety reports, and is

considering label revisions. FDA will keep the public informed of additional findings and actions on this issue.

Related Information

- Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa) Information[1]

Contact FDA

Toll Free
(855) 543-3784, or
(301) 796-3400
druginfo@fda.hhs.gov
Human Drug Information
Division of Drug Information (CDER)
Office of Communications
Feedback Form[2]
10001 New Hampshire Avenue
Hillandale Building, 4th Floor
Silver Spring, MD 20993

Page Last Updated: 09/15/2010

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-88-INFO-FDA (1-888-463-6332)
Email FDA

[Exhibit 160 to Ecklund Declaration]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 0993

NDA 021762

SAFETY LABELING CHANGE AND REMS NOTIFICATION

Merck Sharp & Dohme Corp
Attention: Elinor Chen, Ph.D.
Director, Worldwide Regulatory Affairs
PO Box 2000, RY33-212
Rahway, NJ 07065

Dear Dr. Chen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fosamax Plus D, (alendronate sodium/cholecalciferol) 70 mg/2800 IU and 70 mg/5600 IU tablets.

Sections 505(o)(4) and 505-1 of the FDCA authorize FDA to require holders of approved drug and biological product applications to make safety related labeling changes, and to develop and comply with risk evaluation and mitigation strategies (REMS) based upon new safety information that becomes available after approval of the drug or biological product.

Since Fosamax Plus D was approved on April 7, 2005, we have become aware of a possible increased risk of atypical subtrochanteric and diaphyseal femoral fractures in patients taking bisphosphonates, including Fosamax Plus D, for the treatment and/or prevention of osteoporosis. Recent publications, including the 2010 Report of a Task Force of the American Society for Bone and Mineral Research, suggest that the risk of atypical fractures and diaphyseal femoral fractures increases with increased duration of bisphosphonate exposure. We consider this information to be "new safety information" as defined in section 505-l(b)(3) of the FDCA.

SAFETY LABELING CHANGE

In accordance with section 505(o)(4) of the FDCA, we are notifying you that, based on the new safety information described above, we believe that the information regarding possible increased risk of atypical fractures and diaphyseal femoral fractures should be included in the labeling for bisphosphonates approved for the treatment and/or prevention of osteoporosis as follows:

1. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, under Recent Major Changes: add the following two bullets (underlined):

   Recent Major Changes:

   - Indications and Usage (insert date)
   - Warnings and Precautions (insert date)

2. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, under Indications and Usage: add the following (underlined):

The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis.

3. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, under Warnings and Precautions: add the following bullet (underlined):

   - Atypical femur fractures have been reported. Patients with new thigh or groin pain should be evaluated to rule out a femoral fracture

4. Add the following language to the **INDICATIONS AND USAGE** section of the package insert (underlined):

   1.3 Important Limitations of Use

   The safety and effectiveness of Fosamax Plus D for the treatment of osteoporosis are based on clinical data of four years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

5. Revise the **WARNINGS AND PRECAUTIONS** section of the package insert to add the following paragraphs (underlined) as described below:

   5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fractures:

   Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse

or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no impact to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out a femur fracture. Subjects presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

6. Medication Guide

In addition to the labeling changes described above, you should convert your patient package insert to a Medication Guide for Fosamax Plus D, as shown in the Medication Guide attached (See ENCLOSURES). Your Medication Guide must include information about the serious risk of atypical subtrochanteric and diaphyseal femoral

fractures and will be considered part of the proposed REMS described below.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted. Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT"** or **"SAFETY LABELING CHANGES UNDER 505(o)(4) - CHANGE NOT WARRANTED."**

If you do not submit electronically, please send 5 copies of the submission.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Fosamax Plus D to ensure the benefits of the drug outweigh the risks of atypical subtrochanteric and diaphyseal femoral fractures in patients using bisphosphonates for the treatment and/or prevention of osteoporosis.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Fosamax Plus D poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Fosamax Plus D. FDA has determined that Fosamax Plus D is a product for which patient labeling could help prevent serious adverse effects and/or that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Fosamax Plus D.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Fosamax Plus D.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven

years after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

In accordance with section 505-1, within 30 days of the date of this letter, you must submit a proposed REMS as a supplement to your NDA.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information pertinent to Fosamax Plus D (see Appendix A). Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package

includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the enclosed Medication Guide to each patient." or
- "Dispense the accompanying Medication Guide to each patient."

For administrative purposes, designate the proposed REMS submission "**PROPOSED REMS for NDA 021762/S-###**" and all subsequent submissions related to the proposed REMS "**PROPOSED REMS-AMENDMENT for NDA 021762.**" If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

[See appended electronic signature page]

Audrey Gassman, M.D.
Deputy Director for Safety
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
REMS Appendix A
REMS Appendix B
Medication Guide

Initial REMS Approval: XX/XXXX
Most Recent Modification: XX/XXXX

APPENDIX A: MEDICATION GUIDE REMS TEMPLATE

Application number TRADE NAME
(DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

To inform patients about the serious risks associated with the use of [drug name].

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each [drug name] prescription in accordance with 21 CFR 208.24.

B. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18

months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Include the following paragraph in your REMS:

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, by 18 months, by 3 years and in the 7th year from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

APPENDIX B:

REMS SUPPORTING DOCUMENT TEMPLATE MEDICATION GUIDE REMS

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
   a. Medication Guide
   b. Describe in detail how you will comply with 21 CFR 208.24
   c. Timetable for Submission of Assessments of the REMS (for products approved under and NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

MEDICATION GUIDE

FOSAMAX PLUS D® (FOSS-ah-max PLUS D)

(alendronate sodium/ cholecalciferol)

Tablets

Read the Medication Guide that comes with FOSAMAX PLUS D before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about FOSAMAX PLUS D.

What is the most important information I should know about FOSAMAX PLUS D?

FOSAMAX PLUS D can cause serious side effects including:

1. Esophagus problems
2. Low calcium levels in your blood (hypocalcemia)
3. Bone, joint, or muscle pain
4. Severe jaw bone problems (osteonecrosis)
5. Unusual thigh bone fractures

1. **Esophagus problems.**

   Some people who take FOSAMAX PLUS D may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed.

   - It is import ant that you take FOSAMAX PLUS D exactly as prescribed to help lower your chance of getting esophagus problems.

(See the section "How should I take FOSAMAX PLUS D?")

- Stop taking FOSAMAX PLUS D and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow.

2. **Low calcium levels in your blood (hypocalcemia).**

FOSAMAX PLUS D may lower the calcium levels in your blood. If you have low blood calcium before you start taking FOSAMAX PLUS D, it may get worse during treatment. Your low blood calcium must be treated before you take FOSAMAX PLUS D. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

- Spasms, twitches, or cramps in your muscles
- Numbness or tingling in your fingers, toes, or around your mouth

Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take FOSAMAX PLUS D. Take calcium and vitamin D as your doctor tells you to.

3. **Bone, joint, or muscle pain.**

Some people who take FOSAMAX PLUS D develop severe bone, joint, or muscle pain.

4. **Severe jaw bone problems (osteonecrosis).**

Severe jaw bone problems may happen when you take FOSAMAX PLUS D. Your doctor should examine your mouth before you start FOSAMAX PLUS D. Your doctor may tell you to see your

dentist before you start FOSAMAX PLUS D. It is important for you to practice good mouth care during treatment with FOSAMAX PLUS D.

5. **Unusual thigh bone fractures**.

Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

Call your doctor right away if you have any of these side effects.

What is FOSAMAX PLUS D?

FOSAMAX PLUS D is a prescription medicine used to:

- Treat osteoporosis in women after menopause. FOSAMAX PLUS D increases bone mass and reduces the chance of having a hip or spinal fracture (break).
- Increases bone mass in men with osteoporosis.

FOSAMAX PLUS D should not be used to treat Vitamin D deficiency.

It is not known how long FOSAMAX PLUS D works for the treatment of osteoporosis. You should see your doctor regularly to determine if FOSAMAX PLUS D is still right for you.

FOSAMAX PLUS D is not for use in children.

Who should not take FOSAMAX PLUS D?

Do not take FOSAMAX PLUS D if you:

- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes

- Have low levels of calcium in your blood
- Are allergic to FOSAMAX PLUS D or any of its ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before taking FOSAMAX PLUS D?

Before you start FOSAMAX PLUS D, be sure to talk to your doctor if you:

- Have problems with swallowing
- Have stomach or digestive problems
- Have low blood calcium
- Plan to have dental surgery or teeth removed
- Have kidney problems
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome)
- Are pregnant, or plan to become pregnant. It is not known if FOSAMAX PLUS D can harm your unborn baby.
- Are breast-feeding or plan to breast-feed. It is not known if FOSAMAX PLUS D passes into your milk and may harm your unborn baby.

Especially tell your doctor if you take:

- antacids
- aspirin
- Nonsteroidal Anti-Inflammatory (NSAID) medicines

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Certain medicines may affect how FOSAMAX PLUS D works.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take FOSAMAX PLUS D tablet?

- Take FOSAMAX PLUS D exactly as your doctor tells you.
- **FOSAMAX PLUS D works only if taken on an empty stomach.**
- Take 1 dose of FOSAMAX PLUS D 1 time a week, **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take FOSAMAX PLUS D while you are sitting or standing.
- Take your FOSAMAX PLUS D with plain water only as follows:
- TABLET: Swallow one tablet with a full glass (6-8 oz) of plain water.
- **Do not chew or suck on a tablet of FOSAMAX PLUS D.**
- Do **not** take FOSAMAX PLUS D with mineral water, coffee, tea, soda, or juice.
- Do not take FOSAMAX PLUS D at bedtime.

After swallowing FOSAMAX PLUS D, wait at least 30 minutes:

- Before you lie down. You may sit, stand or walk, and do normal activities like reading.
- Before you take your first food or drink except for plain water.
- Before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down for at least 30 minutes after you take FOSAMAX PLUS D and after you eat your first food of the day.

If you miss a dose of FOSAMAX PLUS D, do not take it later in the day. Take your missed does the next morning and then return to your normal schedule. Do not take 2 doses at the same time.

You should take calcium and vitamin D as directed by your doctor.

If you take too much FOSAMAX PLUS D, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of FOSAMAX PLUS D?

FOSAMAX PLUS D may cause serious side effects.

- See **"What is the most important information I should know about FOSAMAX PLUS D?"**

The most common side effects of FOSAMAX PLUS D are:

- Stomach area (abdominal) pain
- Heartburn
- Constipation
- Diarrhea
- Upset stomach
- Pain in your muscles
- Nausea

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of FOSAMAX PLUS D. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store FOSAMAX PLUS D?

- Store FOSAMAX PLUS D at room temperature, 68°F to 77°F (20°C to 25°C).
- Keep FOSAMAX PLUS D away from light.
- Keep FOSAMAX PLUS D package and tablets dry.
- Store FOSAMAX PLUS D in the original package.

Keep FOSAMAX PLUS D and all medicines out of the reach of children.

General information about the safe and effective use of FOSAMAX PLUS D.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FOSAMAX PLUS D for a condition for which it was not prescribed. Do not give FOSAMAX PLUS D to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about FOSAMAX PLUS D. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about FOSAMAX PLUS D that is written for health professionals.

For more information, go to www.fosamaxplusd.com or call 1-877-408-4699.

What are the ingredients in FOSAMAX PLUS D?

Active ingredient: alendronate sodium and cholecalciferol (D3)

Inactive ingredients: cellulose, lactose, medium chain triglycerides, gelatin, croscarm ellose sodium, sucrose, colloidal silicon dioxide, magnesium stearate, butylated hydroxytoluene, modified food starch, and sodium aluminum silicate.

Manufactured by:
MSD FROSST IBERICA, S.A.
Madrid, Spain

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued Month/Year

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AUDREY L GASSMAN

10/13/2010

[Exhibit 161 to Ecklund Declaration]

To: Chen, Elinor H. <elinor_chen@merck.com>
From: Stiller, Karl <Karl.Stiller@fda.hhs.gov>
CC:
Bcc:
Received Date: 2010-12-16 17:21:34
Subject: Merck bisphosphonate labeling

Dr. Chen: Here is the Fosamax labeling for Merck. The changes include: 1) edits to the W&P for atypical fracture 2) removal of several sentences from 14.1, per DDMAC/OMP discussion 3) significant edits to Highlights to conform to the half page requirement 4) edits to the indication statements in the MG (from increases BMD to helps increase BMD, and from reduces fracture to helps reduce fracture) 5) carton/container comments. Please review and respond by Monday, December 19, 2010. If you agree with the proposed changes, accept tracked changes and send the labeling back to me with a statement indicating your acceptance. Final labeling should be submitted to the applications by December 23, 2010.

LCDR Karl Stiller, R.Ph. Regulatory Health Project Manager Division of Reproductive and Urologic Products Office of Drug Evaluation Ill Center for Drug Evaluation and Research 301-796-1993

Attachments:

Fosamax Plus D DRISK clean MG 11.23.10.doc

Fosamax Plus D DRISK marked up MG 11.23.20.doc
Fosamax Tablets OS DRISK clean MG 11.23.10.doc
Fosamax Tablets OS DRISK marked up MG 11.23.10.doc
Fosamax_Labeling Comments.doc
Fosamax-pi-pas-_FDA_121310.doc
FosamaxPlusD-pi-pas-FDA_121310.doc

MEDICATION GUIDE

FOSAMAX PLUS D® (FOSS-ah-max PLUS D)

(alendronate sodium/cholecalciferol) Tablets

Read the Medication Guide that comes with FOSAMAX PLUS o® before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about FOSAMAX PLUS D.

[DRISK Comment: We revised this MG to reflect the identical class labeling language sent to the Applicant by DRUP on 10/13/10. We deleted the extensive information at the end of the MG concerning Vitamin D and osteoporosis to be consistent with the patient information across the drug class. The Applicant added in this additional information that is not necessary in the Medication Guide. The purpose of the Medication Guide is to educate the patient on the necessary information needed to take the medication safely, not on the disease process the medication treats.]

What is the most important information I should know about FOSAMAX PLUS D?

FOSAMAX PLUS D can cause serious side effects including:

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1. Esophagus problems
2. Low calcium levels in your blood (hypocalcemia)
3. Bone, joint, or muscle pain
4. Severe jaw bone problems (osteonecrosis)
5. Unusual thigh bone fractures

1. Esophagus problems.

Some people who take FOSAMAX PLUS D may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed.

- **It is important that you take FOSAMAX PLUS D exactly as prescribed to help lower your chance of getting esophagus problems. (See the section "How should I take FOSAMAX PLUS D?"**
- **Stop talking FOSAMAX PLUS D and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow.** ***[DRISK Comment: We bolded this information for consistency across bisphosphonate patient labeling.]***

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2. Low calcium levels in your blood (hypocalcemia)

FOSAMAX PLUS D may lower the calcium levels in your blood. If you have low blood calcium before you start taking FOSAMAX PLUS D, it may get worse during treatment. Your low blood calcium must be treated before you take FOSAMAX PLUS D. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

- Spasms, twitches, or cramps in your muscles
- Numbness or tingling in your fingers, toes, or around your mouth

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Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take FOSMAX PLUS D. Take calcium and vitamin D as your doctor tells you to.

3. Bone, joint, or muscle pain.

Some people who take FOSMAX PLUS D develop severe bone, joint, or muscle pain.

4. Severe jaw bone problems (osteonecrosis).

Severe jaw bone problems may happen when you take FOSAMAX PLUS D. Your doctor should examine your mouth before you start FOSAMAX PLUS D. It is important for you to practice good mouth care during treatment with FOSAMAX PLUS D.

5. Unusual thigh bone fractures.

Some people have developed unusual fracture in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

Call your doctor right away if you have any of these side effects.

What is FOSAMAX PLUS D?

FOSAMAX PLUS D is a prescription medicine used to:

- Treat osteoporosis in women after menopause. FOSAMAX PLUS D helps increase bone mass and reduces the chance of having a hip or spinal fracture (break).
- Increase bone mass in men with osteoporosis.

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< # > Esophagus problems¶
< # > Severe jawbone problems (osteonecrosis) ¶
< # > Thigh bone fractures¶
< # > Esophagus problems. ¶
Some people who take FOSAMAX PLUS D may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed. ¶
< # > It is important that you take FOSAMAX PLUS D exactly as prescribed to help lower your chance of getting esophagus problems. (See the section "How should I take FOSAMAX PLUS D?") ¶
< # > Stop taking FOSAMAX PLUS D and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow. ¶ ...[1]

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FOSAMAX PLUS D should not be used to treat vitamin D deficiency.

It is not known how long FOSAMAX PLUS D works for the treatment and prevention of osteoporosis. You should see your doctor regularly to determine if FOSAMAX PLUS D is still right for you.

FOSAMAX PLUS D is not for use in children.

Who should not take FOSAMAX PLUS D?

Do not take FOSAMAX PLUS D if you:

- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes
- Have low levels of calcium in your blood
- Are allergic to FOSAMAX PLUS D or any of its ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before taking FOSAMAX PLUS D?

Before you start FOSAMAX PLUS D, be sure to talk to your doctor if you:

- Have problems with swallowing
- Have stomach or digestive problems
- Have low blood calcium

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- Plan to have dental surgery or teeth removed
- Have kidney problems
- Have sarcoidosis, leukemia, lymphoma. These conditions may cause changes in vitamin D.
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome)
- Are pregnant or plan to become pregnant. It is not known if FOSAMAX PLUS D can harm your unborn baby.
- Are breast-feeding or plan to breast-feed. It is not known if FOSAMAX PLUS D passes into your milk and may harm your baby.

Especially tell your doctor if you take:

- antacids
- aspirin
- Nonsteroidal Anti-Inflammatory (NSAID) medicines

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Certain medicines may affect how FOSAMAX PLUS D works.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

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How should I take FOSAMAX PLUS D tablet?

- Take FOSAMAX PLUS D exactly as your doctor tells you.
- **FOSAMAX PLUS D works only if taken on an empty stomach.**
- Take 1 dose of FOSAMAX PLUS D 1 time a week, **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take FOSAMAX PLUS D while you are sitting or standing.
- Take your FOSAMAX PLUS D tablet with a full glass (6–8 oz) of plain water.
- **Do not chew or suck on a tablet of FOSAMAX PLUS D.**

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< # > Take 1 tablet of FOSAMAX PLUS D **every** week on your chosen day **after** you get up for the day and **before** taking your first food, drink, or other medicine. ¶

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Deleted: FOSAMAX PLUS D works only if it is taken on an empty stomach. ¶ ¶ **Do not chew or suck on a tablet of FOSAMAX PLUS D.**

- Do not take FOSAMAX PLUS D with mineral water, coffee, tea, soda, or juice.
- Do not take FOSAMAX PLUS D at bedtime

After swallowing FOSAMAX PLUS D, wait at least 30 minutes:

- Before you lie down. You may sit, stand or walk, and do normal activities like reading.
- Before you take your first food or drink except for plain water.
- Before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down for at least 30 minutes after you take FOSAMAX PLUS D and after you eat your first food of the day.

If you miss a dose of FOSAMAX PLUS D, do not take it later in the day. Take your missed dose on the next morning after you remember and then return to your normal schedule. Do not take 2 doses on the same day.

You should take calcium and vitamin D as directed by your doctor.

If you take too much FOSAMAX PLUS D, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of FOSAMAX PLUS D?

FOSAMAX PLUS D may cause serious side effects.

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- See **"What is the most important information I should know about FOSAMAX PLUS D?"**

The most common side effects of FOSAMAX PLUS D are:

- Stomach area (abdominal) pain
- Heartburn
- Constipation
- Diarrhea
- Upset stomach
- Pain in your bones, joints, or muscles
- Nausea

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of FOSAMAX PLUS D. For **more** information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report **side** effects to FDA at 1-800-FDA-1088.

How do I store FOSAMAX PLUS D?

- Store FOSAMAX PLUS D at room temperature, 68°F to 77°F (20°C to 25°C).
- Keep FOSAMAX PLUS D away from light.
- Keep FOSAMAX PLUS D package and tablets dry.

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- Store FOSAMAX PLUS D in the original package.

Keep FOSAMAX PLUS D and all medicines out of the reach of children.

General information about the safe and effective use of FOSAMAX PLUS D.

Medicines are sometimes prescribed for conditions other than those listed in a Medication Guide. Do not use FOSAMAX PLUS D for a condition for which it was not prescribed. Do not give FOSAMAX PLUS D to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about FOSAMAX PLUS D. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about FOSAMAX PLUS D that is written for health professionals.

For more information, go to: www.fosamaxplusd.com or call 1-877-408-4699.

What are the ingredients in FOSAMAX PLUS D?

Active ingredients: alendronate sodium and cholecalciferol (vitamin D_3).

Inactive ingredients: cellulose, lactose, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, colloidal silicon dioxide,

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magnesium stearate, butylated hydroxytoluene, modified food starch, and sodium aluminum silicate.

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

By:
FROSST IBERICA, S.A.
28805 Alcalá de Henares
Madrid, Spain

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised Month Year

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Vitamin D is an essential nutrient, required for calcium absorption and healthy bones. The main source is through exposure to summer sunlight, which makes vitamin D in our skin. Winter sunlight in most of the United States is too weak to produce vitamin D. Even in the summer, clothing or sun block can prevent enough sunlight from getting through. In addition, as people age, their skin becomes less able to make vitamin D. Very few foods are natural sources of vitamin D. Some foods, such as milk, some brands of orange juice and breakfast cereals are fortified with vitamin D. ¶ ¶ Too little vitamin D leads to low calcium absorption and low phosphate. These are minerals that make bones strong. Even if you are eating a diet rich in calcium or taking a calcium supplement, your body cannot absorb calcium properly unless you have enough vitamin D. Too little ... ... [11]

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FOSAMAX PLUS D may cause side effects which can be serious including:

Esophagus problems

Severe jawbone problems (osteonecrosis)

Thigh bone fractures

Esophagus problems.

Some people who take FOSAMAX PLUS D may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed.

It is important that you take FOSAMAX PLUS D exactly as prescribed to help lower your chance of getting esophagus problems. (See the section "How should I take FOSAMAX PLUS D?")

Stop taking FOSAMAX PLUS D and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow.

Esophagus problems may get worse if you continue to take FOSAMAX PLUS D.

Severe jawbone problems (osteonecrosis).

Tell your doctor about all of your dental conditions. FOSAMAX PLUS D may cause jawbone problems in some people. Jawbone problems may include infection, and delayed healing after teeth are pulled. It is important for you to practice good oral hygiene and regular

dental care during treatment with FOSAMAX PLUS D.

Thigh bone fractures.

Rarely patients have developed fracture in a specific part of the thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

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drink a full glass of milk and call your doctor right away. Do not try to vomit. Do not lie down.

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Low calcium levels in your blood (hypocalcemia).

If you have been told you have low blood calcium tell your doctor. You

* * *

Numbness or tingling in your fingers, toes, or around mouth

Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels

in your blood, while you take FOSAMAX PLUS D. Take calcium and vitamin D as your doctor tells you.

Bone, joint, or muscle pain.

Some people who take FOSAMAX PLUS D develop bone, joint or muscle pain. Call your doctor if you develop severe bone, joint or muscle pain.

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Mouth sores (ulcers) may occur if the FOSAMAX PLUS D tablet is chewed or dissolved in the mouth.

You may get flu-like symptoms typically at the start of treatment with FOSAMAX PLUS D.

You may get allergic reactions, such as hives or, in rare cases, swelling of your faces, lips, tongue, or throat.

Other side effects are vomiting, a full or bloated feeling in the stomach, black or bloody stools (bowel movements), gas, eye pain, rash that may be made worse by sunlight, hair loss, headache, dizziness, a changed sense of taste, joint swelling or swelling in the hands or legs.

What should I know about Vitamin D?

Vitamin D is an essential nutrient, required for calcium absorption and healthy bones. The main source is through exposure to summer sunlight, which makes vitamin D in our skin. Winter sunlight in most of the United States is too weak to

* * *

foods, such as milk, some brands of orange juice and breakfast cereals fortified with vitamin D.

Too little vitamin D leads to low calcium absorption and low phosphate. These are minerals that make bones strong. Even if you are eating a diet rich in calcium or taking a calcium supplement, your body cannot absorb calcium properly unless you have enough vitamin D. Too little vitamin D may lead to bone loss and osteoporosis.

What should I know about osteoporosis?

Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then a similar

amount of new bone is formed. This balanced process keeps your skeleton healthy and strong.

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause, and may also occur in men. In osteoporosis, bone is removed faster than it is formed, so overall bone mass is lost and bones become weaker. Therefore, keeping bone mass is important to keep your bones healthy. In both men and women, osteoporosis may also be caused by certain medicines called corticosteroids.

At first, osteoporosis usually has no symptoms, but it can cause fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they can make you shorter. Eventually, you spine can curve and your body can become bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause bones to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of ability to move around (mobility).

Who is at risk for osteoporosis?

Many things put people at risk of osteoporosis. The following people have a higher change of getting osteoporosis:

Women who:
Are going through or who are past menopause

Men who:
Are elderly

People who:
Are white (Caucasian) or oriental (Asian)
Do not exercise

Smoke
Drink alcohol often
Take bone thinning medicines (like prednisone or other corticosteroids) for a long time

What can I do to help treat osteoporosis?

In addition to FOSAMAX PLUS D, your doctor may suggest one or more of the following lifestyle changes:

Stop smoking. Smoking may increase your chance of getting osteoporosis.

Reduce the use of alcohol. Too much alcohol may increase the chance of osteoporosis and injuries that can cause fractures.

Exercise regularly. Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries, including fractures. Talk with your doctor before you begin any exercise program.

Eat a balanced diet. Having enough calcium in your diet is important. Your doctor can advise you whether you need to change your diet or take any dietary supplements, such as calcium or additional vitamin D.

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Labeling Comments Regarding NDAs 020560, 021575, and 021762; See accompanying documents with FDA edits (full prescribing information, MG marked and MG clean copies. The clean MG copy contains all appropriate formatting).

Regarding the Full Prescribing Information:

After consideration of all labeling comments received from all sponsors, the Division has accepted two changes to the labeling requested. These changes are:

1) Changed the word "impact" to "trauma" in the first sentence of the second paragraph of the Atypical and Subtrochanteric Femoral Fractures Warning and Precaution.
2) Changed the word "subjects" to "patients" in the second sentence of the third paragraph of the Atypical and Subtrochanteric Femoral Fractures Warning and Precaution.

All other Sponsor proposed changes to this class labeling are not acceptable. This is reflected in the accompanying FDA edited labeling document.

Specifically, for the proposed changes to the Fosamax labels, the term "stress fracture" was considered and was not accepted. The Division believes that for most practitioners, the term "stress fracture" represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use. In addition, the risk factors listed in the proposed changes have not been sufficiently validated to include in labeling at this time.

For labeling in PLR format, edits to the Highlights have been made in order to conform to the half-page requirement.

In addition for the Fosamax Plus D FPI, in order to provide better consistency among the labeling for the bisphosphonate class of products, the following edits were made:

- Section 14.1 Treatment of Postmenopausal Osteoporosis, Effect on Bone Mineral Density: *"Thus, overall FOSAMAX reverses the loss of bone mineral density, a central factor in the progression of osteoporosis."* This sentence has been removed as it is represents an interpretation of the data which may not be true for a given patient. It is best to present the data and allow the prescriber to interpret the results in the context of the patient being treated, from both a safety and an efficacy standpoint. This approach is being consistently applied with all bisphosphonate labels.
- Section 14.1 Treatment of Postmenopausal Osteoporosis, Effect on Bone Mineral Density: *"These data indicate that continued treatment with FOSAMAX is required to maintain the effect of the drug."* This sentence has been removed in light of the ongoing concerns regarding long-term safety and duration of use.

Similar changes have also been made to the non-plr Fosamax FPI where appropriate.

Regarding the Medication Guide:

Both the Division of Reproductive and Urologic Products and the Division of Risk Management do not agree with the proposed dual Medication Guides. The

daily and weekly Medication Guides have again been combined into one document, similar to the others in the bisphosphonate class.

Regarding Carton and Container Labeling:

Fosamax Tablets (NDA 020560/S-060)

Carton labeling — 70 mg tablets (Four count):

The Medication Guide statement lacks prominence. Revise and increase the font size of the Medication Guide statement to at least that of the information on osteoporosis presented in the same panel.

35 mg and 70 mg Card Backs:

"For the treatment of osteoporosis in postmenopausal women. Osteoporosis is a disease that causes bones to become thin, weak and easy to break. That's why it is important you take *Once Weekly* FOSAMAX to help protect your bones.

These claims are considered promotional and require fair balance presentation. The claims should be deleted or presented with adequate risk information to provide fair balance.

Container labels — 10 mg tablets (30 count):

Relocate the Medication Guide statement to the principal display panel. To provide space for the Medication Guide statement, relocate the "Each tablet contains..." statement to the side panel. If additional side panel space is needed, delete the "For important instructions for use..." statement on the side panel.

Fosamax Plus D Tablets (NDA 021762)

General Comment

We note that some of the carton/container labels state "Fosamax Plus" as the proprietary name. Please consider revising the tradename to "Fosamax Plus D," where applicable, for accuracy.

Carton labeling — 70 mg/2800 international units and 70 mg/5600 international units tablets (Four count):

The Medication Guide statement lacks prominence. Revise and increase the font size of the Medication Guide statement to at least that of the "Usage Dosage" statement.

Carton/Container Label

U.S. Complimentary Carton 1 count 5600 IU:

"For treatment of osteoporosis in postmenopausal women"

This claim is considered promotional and requires adequate fair balance presentation. We note that statement, "Side effects in studies usually have been mild and generally have not caused patients to stop taking FOSAMAX PLUS [D]. The most commonly reported side effect was abdominal (stomach) pain." However, this statement is not only inadequate in terms of a balanced risk presentation, but also minimizes the risks associated with Fosamax Plus D, by failing to include (but not limited to) hypocalcemia, severed irritation of upper gastrointestinal mucosa, and osteonecrosis of the jaw. Delete this claim or present adequate risk information in conjunction with this claim.

The U.S. Complimentary Carton 1 count 5600 IU label presents an image of a woman on the carton label. This image is misleading because Fosamax Plus is also indicated for "treatment to increase bone mass in men with osteoporosis" and may cause confusion if this carton is distributed to a male patient. In addition, this image suggests that this drug is used for a particular patient population, which is also considered promotional in nature. Consider removing this image from this container label.

Container 10 — Physician sample (1 ct) (outside):

"For the treatment of osteoporosis in postmenopausal women and to help ensure adequate vitamin D nutrition."

This claim is considered promotional and requires fair balance. We note the statement, "side effects in studies usually have been mild and generally have not caused patients to stop taking FOSAMAX PLUS [D]. The most commonly reported side effect was abdominal (stomach) pain." However, this statement is not only inadequate in terms of a balanced risk presentation, but also minimizes the risks associated with Fosamax Plus, by failing to include (but not limited to) hypocalcemia, severe irritation of upper gastrointestinal mucosa, and osteonecrosis of the jaw. Delete this claim or present adequate risk information in conjunction with this claim.

The Physician sample (1 ct) (outside) label presents an image of a woman on the container label. This image is misleading because

Fosamax Plus D is also indicated for "treatment to increase bone mass in men with osteoporosis" and may cause confusion if this sample pack is distributed to a male patient. In addition, this image suggests that this drug is used for a particular patient population, which is also considered promotional in nature. Please consider removing this image from this container label.

Fosamax Oral Solution (NDA 021575/S-020)

Carton Labeling — 70 mg bottles (Four count):

The Medication Guide statement lacks prominence. Revise and increase the font size of the Medication Guide statement to at least that of the information on osteoporosis presented in the same panel.

To provide adequate space, delete the country of origin statement from the principal display panel as it is duplicative to information added to the side panel.

"For the treatment of osteoporosis in postmenopausal women. Osteoporosis is a disease that causes bones to become thin, weak and easy to break. That's why it is important you take *Once Weekly* FOSAMAX to help protect your bones."

These claims are considered promotional and require fair balance presentation. The claims should be deleted or presented with adequate risk information to provide fair balance.

Container label

The information on the label appears crowded which makes the Medication Guide statement

difficult to find. Therefore, delete the country of origin statement from the principal display panel to allow for the increase in prominence of the Medication Guide statement.

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

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FOSAMAX®

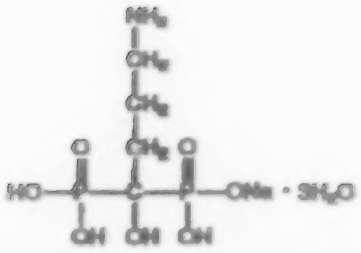
(ALENDRONATE SODIUM) TABLETS
AND ORAL SOLUTION

DESCRIPTION

FOSAMAX® is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

The empirical formula of alendronate sodium is $C_4H_{12}NNaO_7P_23H_20$ and its formula weight is 325.12. The structural formula is:



Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Tablets FOSAMAX for oral administration contain 6.53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscamellose sodium, and magnesium stearate. Tablets FOSAMAX 10 mg also contain carnauba wax.

Each bottle of the oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 70 mg of free acid. Each bottle also contains the following inactive ingredients: raspberry flavor, and purified water. Added as preservatives are sodium propylparaben 0.0225% and sodium butylparaben 0.0075%.

CLINICAL PHARMACOLOGY

Mechanism of Action

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled

border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [^{3}H]alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]alendronate in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While incorporated in bone matrix, alendronate is not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

Pharmacokinetics

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.65% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg table in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

FOSAMAX 70 mg oral solution and FOSAMAX 70 mg tablet are equally bioavailable.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 40 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1mg/kg IV administration but it then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/Ml) FOR ANALYTICAL DETECTION. Protein binding in human plasma is approximately 78%.

Metabolism

There is no evidence that alendronate is metabolized in animals or humans.

Excretion

Following a single IN dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a

single 10 mg IV dose, the renal clearance of alendronate was 71 Ml/MIN (64, 78; 90% CONFIDENCE INTERVAL [CI], and systemic clearance did not exceed 200 Ml/MIN. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with FOSAMAX (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations

Pediatric: The oral bioavailability in children was similar to that observed in adults; however, FOSAMAX is not indicated for use in children (see PRECAUTIONS, *Pediatric Use*).

Gender: Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Geriatric: Bioavailability and disposition (urinary excretion) were similar in elderly and younger patients. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks

dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearances 35 to 60 mL/min). **FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience with alendronate in renal failure.**

Hepatic Insufficiency: As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary. *Drug Interactions* (also see PRECAUTIONS, *Drug Interactions*)

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.

Pharmacodynamics

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Osteoporosis in postmenopausal women

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral (spinal) fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant portion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to 90, the risk of hip fracture in white women increases 50-fold and the risk of vertebral fracture 15- to 30-fold. It is estimated that approximately 40% of 50-year old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent

inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with FOSAMAX 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received FOSAMAX 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with FOSAMAX. In osteoporosis treatment studies FOSAMAX 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25 to 30% to reach a plateau after 6 to 12 months. In osteoporosis prevention studies FOSAMAX 5 mg/day decreased osteocalcin and total serum alkaline phosphatase by approximately 40% and 15%, respectively. Similar reductions in the rate of bone turnover were observed in postmenopausal women during one-year studies with once weekly FOSAMAX 70 mg for the treatment of osteoporosis and once weekly FOSAMAX 35 mg for

the prevention of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with FOSAMAX. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of FOSAMAX 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment; however, serum phosphate returned toward prestudy levels during years three through five. Similar reductions were observed with FOSAMAX 5 mg/day. In one-year studies with once weekly FOSAMAX 35 and 70 mg, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to FOSAMAX but also a decrease in renal phosphate reabsorption.

Osteoporosis in men

Treatment of men with osteoporosis with FOSAMAX 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a one-year study in men with osteoporosis receiving once weekly FOSAMAX 70 mg.

Glucocorticoid-induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs both in males and females of all ages. Osteoporosis occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of up to two years' duration, FOSAMAX 5 and 10 mg/day reduced cross-linked N-telopeptides of type I collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 15 to 30% and 8 to 18%, respectively. As a result of inhibition of bone resorption, FOSAMAX 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1 to 2%) and serum phosphate (approximately 1 to 8%).

Paget's disease of bone

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical

index of disease activity, provides an objective measure of disease severity and response to therapy.

FOSAMAX decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, FOSAMAX 40 mg once daily for six months produced significant decreases in serum alkaline phosphatase as well as in urinary markers of bone collagen degradation. As a result of the inhibition of bone resorption, FOSAMAX induced generally mild, transient, and asymptomatic decreases in serum calcium and phosphate.

Clinical Studies

Treatment of osteoporosis

Postmenopausal women

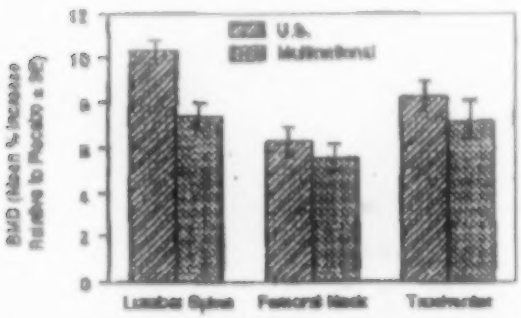
Effect on bone mineral density

The efficacy of FOSAMAX 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of a least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration. These included two three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 10 mg/day relative to

placebo-treated patients at three years for each of these studies.

Osteoporosis Treatment Studies in
Postmenopausal Women

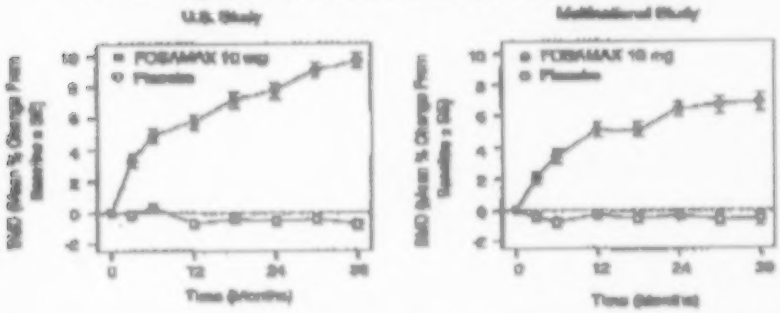
Increase in BMD
FOSAMAX 10 mg/day at Three Years



At three years significant increases in BMD, relative to baseline and placebo, were seen at each measurement site in each study in patients who received FOSAMAX 10 mg/day. Total body BMD also increased significantly in each study, suggesting that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the three years of treatment. (See figures below for lumbar spine results.) In the two-year extension of these studies, treatment of 147 patients with FOSAMAX 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total

body were maintained. FOSAMAX was similarly effective regardless of age, race, baseline rate of bone turnover, and baseline BMD in the range studied (at least 2 standard deviations below the premenopausal mean).

Osteoporosis Treatment Studies in Postmenopausal Women
Time Course of Effect of FOSAMAX 10 mg/day Versus Placebo:
Lumbar Spine BMD Percent Change From Baseline



In patients with postmenopausal osteoporosis treated with FOSAMAX 10 mg/day for one or two years, the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those of the placebo groups.

Deleted: Thus, overall FOSMAX reverses the loss of bone mineral density, a central factor in the progression of osteoporosis

Deleted: These data indicate that continued treatment with FOSAMAX is required to maintain the effect of the drug.

The therapeutic equivalence of once weekly FOSAMAX 70 mg (n=519) and FOSAMAX 10 mg daily (n=370) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the 70-mg once-weekly group (n=440) and 5.4% (5.0, 5.8%; 95% CI) in the 10-mg daily group (n=330). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Effect on fracture incidence

Data on the effects of FOSAMAX on fracture incidence are derived from three clinical studies: 1) U.S. and Multinational combined: a study of patients with a BMD T-score at or below minus 2.5 with or without a prior vertebral fracture, 2) Three-Year Study of the Fracture Intervention Trial (FIT): a study of patients with at least one baseline vertebral fracture, and 3) Four-Year Study of FIT: a study of patients with low bone mass but without a baseline vertebral fracture.

To assess the effects of FOSAMAX on the incidence of vertebral fractures (detected by digitized radiography; approximately one third of these were clinically symptomatic), the U.S. and Multinational studies were combined in an analysis that compared placebo to the poled dosage groups of FOSAMAX (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a statistically significant reduction in the proportion of patients

treated with FOSAMAX experiencing one or more new vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%; a 48% relative risk reduction). A reduction in the total number of new vertebral fractures (4.2 v. 11.3 per 100 patients) was also observed. In the pooled analysis, patients who received FOSAMAX had a loss in stature that was statistically significantly less than was observed in those who received placebo (-3.0 mm vs. -4.6 mm).

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline radiographic vertebral fracture and the Four-Year Study of patients with low bone mass but without a baseline vertebral fracture. In both studies of FIT, 96% of randomized patients completed the studies (i.e., had a closeout visit at the scheduled end of the study); approximately 80% of patients were still taking study medication upon completion.

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 2027-patient study (FOSAMAX, n=1022; placebo, n=1005) demonstrated that treatment with FOSAMAX resulted in statistically significant reductions in fracture incidence at three years as shown in the table below.

[see next page for table]

Effect of FOSAMAX on Fracture Incidence in the Three-Year Study of FIT
(patients with vertebral fracture at baseline)

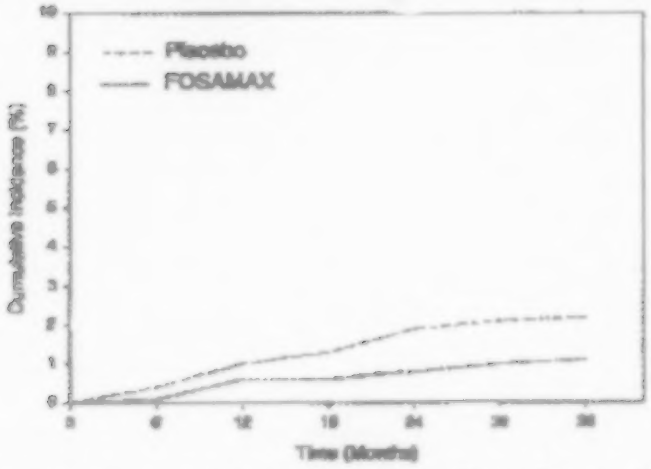
	Percent of Patients			
	FOSAMAX (n=1022)	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %
Patients with:				
Vertebral fractures (diagnosed by X-ray)[†]				
≥ 1 new vertebral fracture	7.9	15.0	7.1	47***
≥ 2 new vertebral fractures	0.8	4.9	4.4	90***
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	13.8	18.1	4.3	28[‡]
≥ 1 clinical (symptomatic) vertebral fracture	2.3	5.0	2.7	54**
Hip fracture	1.1	2.2	1.1	51*
Wrist (forearm) fracture	2.2	4.1	1.9	48*

[†]Number evaluable for vertebral fractures: FOSAMAX, n=984; placebo, n=966
*p<0.05, **p<0.01, ***p<0.001, [‡]p=0.007

Furthermore, in this population of patients with baseline vertebral fracture, treatment with FOSAMAX significantly reduced the incidence of hospitalizations (25.0% vs. 30.7%).

In the Three-Year Study of FIT, fractures of the hip occurred in 22 (2.2%) of 1005 patients on placebo and 11 (1.1%) of 1022 patients on FOSAMAX, p=0.047. The figure below displays the cumulative incidence of hip fractures in this study.

Cumulative Incidence of Hip Fractures in the
Three-Year Study of FIT
(patients with radiographic vertebral fracture at baseline)



Fracture Intervention Trial: Four-Year Study (patients with low bone mass but without a baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 4432-patient study (FOSAMAX, n=2214; placebo, n=2218) further investigated the reduction in fracture incidence due to FOSAMAX. The intent of the study was to recruit women with osteoporosis, defined as a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the table below for the patients with osteoporosis.

[see next page for table]

Effect of FOSAMAX on Fracture Incidence in Osteoporotic† Patients in the Four-Year Study of FIT
(patients without vertebral fracture at baseline)

	Percent of Patients			
	FOSAMAX (n=1545)	Placebo (n=1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk (%)
Patients with:				
Vertebral fractures (diagnosed by X-ray)‡				
≥ 1 new vertebral fracture	2.5	4.8	2.3	48***
≥ 2 new vertebral fractures	0.1	0.9	0.8	79*
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	12.9	16.2	3.3	22**
≥ 1 clinical (symptomatic) vertebral fracture	1.8	1.8	0.0	41 (ns)***
Hip fracture	1.9	1.4	0.4	29 (ns)***
Wrist (forearm) fracture	3.9	3.8	-0.1	NS***

†Baseline femoral neck BMD at least 2 SD below the mean for young adult women
‡Number evaluable for vertebral fractures: FOSAMAX, n=1429; placebo, n=1428
***Not significant. This study was not powered to detect differences at these sites.
*p=0.035, ** p=0.01, ***p<0.001

Fracture results across studies

In the Three-Year Study of FIT, FOSAMAX reduced the percentage of women experiencing at least one new radiographic vertebral fracture from 15.0% to 7.9% (47% relative risk reduction, p<0.001); in the Four-Year Study of FIT, the percentage was reduced from 3.8% to 2.1% (44% relative risk reduction, p=0.001); and in the combined U.S./Multinational studies, from 6.2% to 3.2% (48% relative risk reduction, p=0.034).

FOSAMAX reduced the percentage of women experiencing multiple (two or more) new vertebral fractures from 4.2% to 0.6% (87% relative risk reduction, p<0.001) in the combined U.S./Multinational studies and from 4.9% to 0.5% (90% relative risk reduction, p<0.001) in the Three-Year Study of FIT. In the Four-Year Study of FIT, FOSAMAX reduced the percentage of osteoporotic women experiencing multiple vertebral fractures from 0.6% to 0.1% (78% relative risk reduction, p=0.035).

Thus, FOSAMAX reduced the incidence of radiographic vertebral fractures in osteoporotic

women whether or not they had a previous radiographic vertebral fracture.

FOSAMAX, over a three- or four-year period, was associated with statistically significant reductions in loss of height vs. placebo in patients with and without baseline radiographic vertebral fractures. At the end of the FIT studies the between-treatment group differences were 3.2 mm in the Three-Year Study and 1.3 mm in the Four-Year Study.

Bone Histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with FOSAMAX at doses ranging from 1 to 20 mg/day for one, two, or three years revealed normal mineralization and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in rats and baboons exposed to long-term alendronate treatment, support the conclusion that bone formed during therapy with FOSAMAX is of normal quality.

Men

The efficacy of FOSAMAX in men with hypogonadal or idiopathic osteoporosis was demonstrated in two clinical studies.

A two-year, double-blind, placebo-controlled, multicenter study of FOSAMAX 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). All patients in the trial had either: 1) a BMD T-score $\leq$-2 at the femoral neck and $\leq$-1 at the lumbar spine, or 2) a baseline osteoporotic fracture and a BMD T-score $\leq$-1 at the femoral neck. At two years, the mean increases relative to placebo in BMD in men receiving FOSAMAX 10 mg/day were

significant at the following sites: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Treatment with FOSAMAX also reduced height loss (FOSAMAX, -0.6 mm vs. placebo, -2.4 mm).

A one-year, double-blind, placebo-controlled, multicenter study of once weekly FOSAMAX 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, 2) a BMD –score ≤-2 at the lumbar spine and ≤-1 at the femoral neck, or 3) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At one year, the mean increases relative to placebo in BMD in men receiving FOSAMAX 70 mg once weekly were significant at the following sites: lumbar spine, 2.8%; femoral neck, 1.9%; trochanter, 2.0%; and total body, 1.2%. These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.

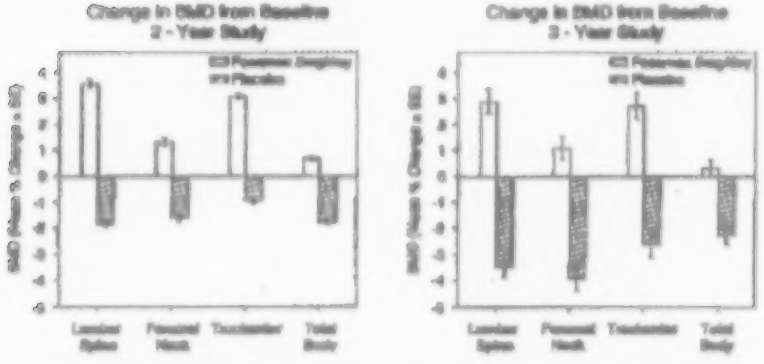
In both studies, BMD responses were similar regardless of age (≥65 years vs. <65 years), gonadal function (baseline testosterone <9 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score ≤-2.5 vs. >2.5).

Prevention of osteoporosis in postmenopausal women

Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal women 40-60 years of age. One thousand six hundred nine patients (FOSAMAX 5 mg/day; n=498) who were at least six months postmenopausal were entered into a two-year study without regard to their baseline BMD. In the other study, 447 patients (FOSAMAX 5 mg/day; n=88), who

were between six months and three years postmenopause, were treated for up to three years. In the placebo-treated patients BMD losses of approximately 1% per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, FOSAMAX 5 mg/day prevented bone loss in the majority of patients and induced significant increases in mean bone mass at each of these sites (see figures below). In addition, FOSAMAX 5 mg/day reduced the rate of bone loss at the forearm by approximately half relative to placebo. FOSAMAX 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.

Osteoporosis Prevention Studies in Postmenopausal Women



The therapeutic equivalence of once weekly FOSAMAX 35 mg (n=362) and FOSAMAX 5 mg daily (n=361) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women without osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 2.9% (2.6, 3.2%; 95% CI) in the 35-mg once-weekly group (n=307) and 3.2% (2.9, 3.5%;

95% CI) in the 5-mg daily group (n=298). The two treatments groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Bone histology

Bone histology was normal in the 28 patient biopsied at the end of three years who received FOSAMAX at doses of up to 01 mg/day.

Concomitant use with estrogen/hormone replacement therapy (HRT)

The effects on BMD of treatment with FOSAMAX 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomized postmenopausal osteoporotic women (n=425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either estrogen or FOSAMAX alone (both 6.0%).

The effects on BMD when FOSAMAX was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n=428). The addition of FOSAMAX 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favorable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD.

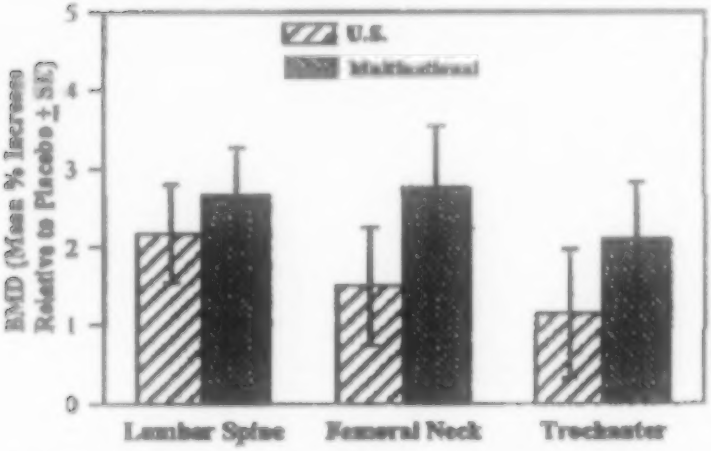
Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with FOSAMAX and HRT, 94% on FOSAMAX alone, and 78% on HRT alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence and fracture healing have not been studied.

Glucocorticoid-induced osteoporosis

The efficacy of FOSAMAX 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year, double-blind, randomized, placebo-controlled, multicenter studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational [which also included FOSAMAX 2.5 mg/day]). These studies enrolled 232 and 328 patients, respectively, between the ages of 17 and 83 with a variety of glucocorticoid-requiring diseases. Patients received supplemental calcium and vitamin D. The following figure shows the mean increases relative to placebo in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 5 mg/day for each study.

[see graph on next page]

Studies in Gincocorticoid – Treated Patients
Increase in BMD
FOSAMAX 5 mg/day at One Year



After one year, significant increases relative to placebo in BMD were seen in the combined studies at each of these sites in patients who received FOSAMAX 5 mg/day. In the placebo-treated patients, a significant decrease in BMD occurred at the femoral neck (-1.2%), and smaller decreases were seen at the lumbar spine and trochanter. Total body BMD was maintained with FOSAMAX 5 mg/day. The increases in BMD with FOSAMAX 10 mg/day were similar to those with FOSAMAX 5 mg/day in all patients except for postmenopausal women not receiving estrogen therapy. In these women, the increases (relative to placebo) with FOSAMAX 10 mg/day were greater than those with FOSAMAX 5 mg/day at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. FOSAMAX was effective regardless of dose r duration of glucocorticoid use. In addition, FOSAMAX was similarly effective regardless of age (<65 vs. ≥65 years), race (Caucasian vs. other races),

gender, underlying disease, baseline BMD, baseline bone turnover, and use with a variety of common medications.

Bone histology was normal in the 49 patients biopsied at the end of one year who received FOSAMAX at doses of up to 10 mg/day.

Of the original 560 patients in these studies, 208 patients who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year double-blind extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with FOSAMAX 5 and 10 mg/day, respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.

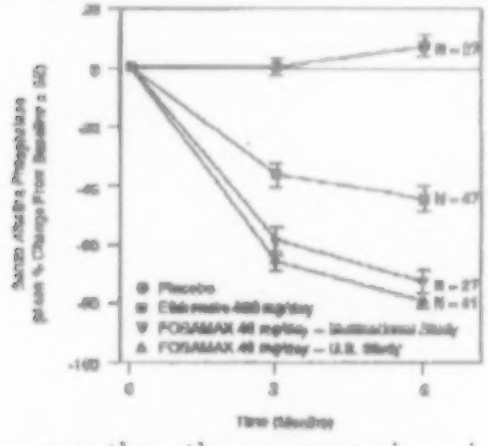
After one year, 2.3% of patients treated with FOSAMAX 5 or 10 mg/day (pooled) vs. 3.7% of those treated with placebo experienced a new vertebral fracture (not significant). However, in the population studied for two years, treatment with FOSAMAX (pooled dosage groups: 5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) significantly reduced the incidence of patients with a new vertebral fracture (FOSAMAX 0.7% vs. placebo 6.8%).

Paget's disease of bone

The efficacy of FOSAMAX 40 mg once daily for six months was demonstrated in two double-blind clinical studies of male and female patients with moderate to severe Paget's disease (alkaline phosphatase at least twice the upper limit of normal): a placebo-controlled, multinational study and a U.S. comparative study with etidronate disodium 400 mg/day. The following

figure shows the mean percent changes from baseline in serum alkaline phosphatase for up to six months of randomized treatment.

Studies in Paget's Disease of Bone
Effect on Serum Alkaline Phosphatase of FOSAMAX 40 mg/day Versus Placebo of Etidronate



At six months the suppression in alkaline phosphatase in patients treated with FOSAMAX was significantly greater than that achieved with etidronate and contrasted with the complete lack of response in placebo-treated patients. Response (defined as either normalization of serum alkaline phosphatase or decrease from baseline ≥60%) occurred in approximately 85% of patients treated with FOSAMAX in the combined studies vs. 30% in the etidronate group and 0% in the placebo group. FOSAMAX was similarly effective regardless of age, gender, race, prior use of other bisphosphonates, or baseline alkaline phosphatase within the range studied (at least twice the upper limit of normal).

Bone histology was evaluated in 33 patients with Paget's disease treated with FOSAMAX 40 mg/day for

6 months. As in patients treated for osteoporosis (see *Clinical Studies, Treatment of osteoporosis in postmenopausal women, Bone histology*), FOSAMAX did not impair mineralization, and the expected decrease in the rate of bone turnover was observed. Normal lamellar bone was produced during treatment with FOSAMAX, even where preexisting bone was woven and disorganized. Overall, bone histology data support the conclusion that bone formed during treatment with FOSAMAX is of normal quality

ANIMAL PHARMACOLOGY

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

INDICATIONS AND USAGE

FOSAMAX is indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women
  - For the treatment of osteoporosis, FOSAMAX increases bone mass and reduces the incidence of fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the

premenopausal mean) or by the presence or history of osteoporotic fracture. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics*.)

- For the prevention of osteoporosis, FOSAMAX may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture.

  Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of FOSAMAX for prevention of osteoporosis.

- Treatment to increase bone mass in men with osteoporosis
- Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density (see PRECAUTIONS, *Glucocorticoid-induced osteoporosis*). Patients

treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.

- Treatment of Paget's disease of bone in men and women

[continued on next page with edits]

- Treatment is indicated in patients with Paget's disease of bone having alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

The safety and effectiveness of FOSAMAX for the treatment of osteoporosis are based on clinical data of four years duration. The optimal duration for use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

Deleted: studies

Deleted: demonstrating fracture risk reduction

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes (see WARNINGS)
- Patients at increased risk of aspiration should not receive FOSAMAX oral solution.
- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, *General*)

WARNINGS

FOSAMAX, like other bisphosphonates administered orally, may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the

underlying disease, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis, or ulcers).

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates including FOSAMAX. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates including FOSAMAX and/or who fail to swallow oral bisphosphonates including FOSAMAX with the recommended full glass (6-8 oz) of water, and/or who continue to take oral bisphosphonates including FOSAMAX after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to mental disability, therapy with FOSAMAX should be used under appropriate supervision.

There have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

General

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FOSAMAX.

Presumably due to the effects of FOSAMAX on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Musculoskeletal Pain

In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking

bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). This category of drugs incudes FOSAMAX (alendronate). Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrent of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups.

Dental

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including FOSAMAX. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (e.g., tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures).

For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk for ONJ. Clinical judgment of the treating physician and/or oral surgeon should guide

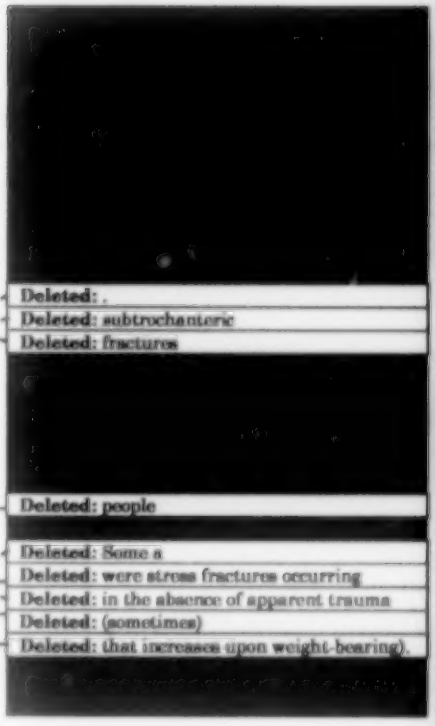
the management plan of each patient based on individual benefit/risk assessment.

Patients who develop osteonecrosis of the jaw while on bisphosphonate therapy should receive care by an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma, fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from below the lesser trochanter to above the supracondular flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.



Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Renal insufficiency

FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Glucocoticoid-induced osteoporosis

The risk versus benefit of FOSAMAX for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see INDICATIONS AND USAGE). Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

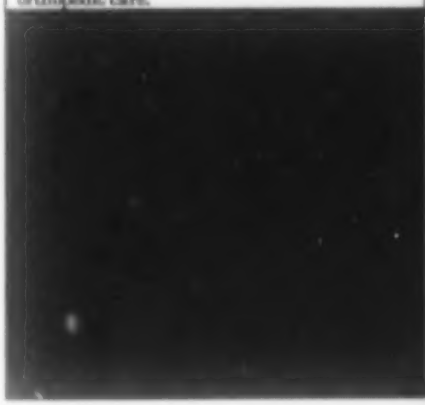
A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined FOSAMAX and glucocorticoid treatment.

Deleted: similar symptoms

Deleted: evaluated to rule out a stress fracture. Patients presenting with an atypical fracture should also be

Deleted: Incomplete stress

Deleted: Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care.



The efficacy of FOSAMAX for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of FOSAMAX has been established in studies of two years' duration. The greatest increase in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of FOSAMAX beyond two years has not been studied.

The efficacy of FOSAMAX in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in postmenopausal women. The efficacy for prevention of non-vertebral fractures has not been demonstrated.

Information for Patients

General

Physicians should instruct their patients to read the Medication Guide before starting therapy with FOSAMAX and to reread it each time the prescription is renewed.

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Dosing Instructions

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when it is

taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Absorption*).

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of FOSAMAX with a full glass of water (6-8 oz). To facilitate gastric emptying patients should drink at least 2 oz (a quarter of a cup) of water after taking FOSAMAX oral solution. Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking FOSAMAX and consult their physician.

Patients should be instructed that if they miss a dose of once weekly FOSAMAX, they should take one dose on the morning after they remember. They should not take two doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.

Drug Interactions (also see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Drug Interactions)*

Estrogen/hormone replacement therapy (HRT)

Concomitant use of HRT (estrogen ± progestin) and FOSAMAX was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence have not been studied (see CLINICAL PHARMACOLOGY, *Clinical Studies, Concomitant use with estrogen/hormone replacement therapy (HRT)* and ADVERSE REACTIONS, *Clinical Studies, Concomitant use with estrogen/hormone replacement therapy*).

Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of FOSAMAX. Therefore, patients must wait at least one-half hour after taking FOSAMAX before taking any other oral medications.

Aspirin

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of FOSAMAX greater than 10 mg and aspirin-containing products.

Nonsteroidal Anti-inflammatory Drugs (NSA/Ds)

FOSAMAX may be administered to patients taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIOs, the incidence of upper gastrointestinal adverse events was similar in patients taking FOSAMAX 5 or 10 mg/day compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with FOSAMAX.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oralcarcinogenicity study at doses of 1 and 3. 75 mglkg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the in vitro microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo*

chromosomal aberration assay in mice. In an in vitro chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Pregnancy

Pregnancy Category C:

Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg!m2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths)

occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

There are no studies in pregnant women. FOSAMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in

human milk, caution should be exercised when FOSAMAX is administered to nursing women.

Pediatric Use

The efficacy and safety of FOSAMAX were examined in a randomized, double-blind, placebo-controlled two-year study of 139 pediatric patients, aged 4-18 years, with severe osteogenesis imperfecta. One-hundred-and-nine patients were randomized to 5 mg FOSAMAX daily (weight <40 kg) or 10 mg FOSAMAX daily (weight ≥40 kg) and 30 patients to placebo. The mean baseline lumbar spine BMD Z-score of the patients was -4.5. The mean change in lumbar spine BMD Z-score from baseline to Month 24 was 1.3 in the FOSAMAX-treated patients and 0.1 in the placebo-treated patients. Treatment with FOSAMAX did not reduce the risk of fracture. Sixteen percent of the FOSAMAX patients who sustained a radiologically-confirmed fracture by Month 12 of the study had delayed fracture healing (callus remodeling) or fracture non-union when assessed radiographically at Month 24 compared with 9% of the placebo-treated patients. In FOSAMAX-treated patients, bone histomorphometry data obtained at Month 24 demonstrated decreased bone turnover and delayed mineralization time; however, there were no mineralization defects. There were no statistically significant differences between the FOSAMAX and placebo groups in reduction of bone pain.

FOSAMAX is not indicated for use in children.

(For clinical adverse experiences in children, see ADVERSE REACTIONS, *Clinical Studies, Osteogenesis Imperfecta.*)

Geriatric Use

Of the patients receiving FOSAMAX in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years of age and 17% (n=550) were ≥75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 45%, 54%, 37%, and 70%; respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Clinical Studies

In clinical studies of up to five years in duration adverse experiences associated with FOSAMAX usually were mild, and generally did not require discontinuation of therapy.

FOSAMAX has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of osteoporosis

Postmenopausal women

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention

Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: FOSAMAX, 3.2%; placebo, 2.7%. In these study populations, 49-54% had a history of gastrointestinal disorders at baseline and 54-89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX or placebo are presented in the following table.

[illegible]

Rarely, rash and erythema have occurred.

One patient treated with FOSAMAX (10 mg/day), who had a history of peptic ulcer disease and

gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of FOSAMAX in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with FOSAMAX 1 0 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 70 mg and FOSAMAX 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group are presented in the following table.

[see next page for table]

Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients		
	Once Weekly FOSAMAX 70 mg % (n=519)	FOSAMAX 10 mg/day % (n=370)
Gastrointestinal		
abdominal pain	3.7	3.8
dyspepsia	2.7	2.2
acid regurgitation	1.9	2.4
nausea	1.9	2.4
abdominal distention	1.9	1.4
constipation	0.8	1.9
flatulence	0.4	1.6
gastritis	0.2	1.1
gastric ulcer	0.8	1.1
Musculoskeletal		
musculoskeletal (bone, muscle, joint) pain	2.9	3.2
muscle cramp	0.2	1.1

Men

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 10 mg/day and a one-year study of once weekly FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for FOSAMAX 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly FOSAMAX 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥2% of patients treated with either FOSAMAX or placebo are presented in the following table.

Osteoporosis Studies in Men Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2% of Patients				
	Two-year Study		One-year Study	
	FOSAMAX 10 mg/day % (n=146)	Placebo % (n=95)	Once Weekly FOSAMAX 70 mg % (n=139)	Placebo % (n=99)
Gastrointestinal				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.9	0.0
dyspepsia	3.4	0.0	2.9	1.7
diarrhea	1.4	1.1	2.9	0.0
abdominal pain	2.1	1.1	0.0	3.4
nausea	2.1	0.0	0.0	0.0

Prevention of osteoporosis in postmenopausal women

The safety of FOSAMAX 5 mg/day in postmenopausal women 40-60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive FOSAMAX for either two or three years. In these studies the overall safety profiles of FOSAMAX 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with FOSAMAX 5 mg/day and 5.7% of 648 patients treated with placebo.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 35 mg and FOSAMAX 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either once weekly FOSAMAX 35 mg, FOSAMAX 5 mg/day or placebo are presented in the following table.

Osteoporosis Prevention Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	Two/Three-Year Studies		One-Year Study	
	FOSAMAX 5 mg/day % (n=642)	Placebo % (n=648)	FOSAMAX 5 mg/day % (n=381)	Once Weekly FOSAMAX 35 mg % (n=370)
Gastrointestinal				
dyspepsia	1.9	1.4	2.9	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.9	1.4
diarrhea	1.1	1.7	1.3	0.8
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.8	2.2

Concomitant use with estrogen/hormone replacement therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with FOSAMAX 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Treatment of glucocorticoid-induced osteoporosis

In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX 5 or 10 mg/day or placebo are presented in the following table.

[illegible]

	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]
[illegible]			
[illegible]	3.2	1.8	6.0
[illegible]	2.6	1.8	1.3
[illegible]	1.3	0.9	0.0
[illegible]	1.3	0.6	0.0
[illegible]	0.6	1.2	0.6
[illegible]	0.0	0.6	1.9
[illegible]			
[illegible]	0.6	0.0	1.3

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year.

Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo.

Osteogenesis Imperfecta

FOSAMAX is not indicated for use in children.

The overall safety profile of FOSAMAX in OI patients treated for up to 24 months was generally similar to that of adults with osteoporosis treated with FOSAMAX. However, there was an increased occurrence of vomiting in OI patients treated with FOSAMAX compared to placebo. During the 24-month treatment period, vomiting was observed in 32 of 109

(29.4%) patients treated with FOSAMAX and 3 of 30 (10%) patients treated with placebo.

In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of FOSAMAX 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration. These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with an acute-phase response that has been reported in patients receiving bisphosphonates, including FOSAMAX. See ADVERSE REACTIONS, *Post-Marketing Experience, Body as a Whole.*

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with FOSAMAX, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, *Information for Patients*, and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection with delayed healing, has been reported rarely (see PRECAUTIONS, *Dental*). *Musculoskeletal:* bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, *Musculoskeletal Pain*); joint swelling; low-energy femoral shaft and subtrochanteric fractures (see PRECAUTIONS, *Atypical Subtrochanteric and Diaphyseal Femoral Fractures).*

Nervous system: dizziness and vertigo.

Skin: rash (occasionally with photosensitivity}, pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mglkg (4000 mg/m^2).

No specific information is available on the treatment of overdosage with FOSAMAX. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

FOSAMAX must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only (see PRECAUTIONS, *Information for Patients*). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of FOSAMAX (see PRECAUTIONS, Drug Interactions). Waiting less than 30 minutes, or taking FOSAMAX with food, beverages (other than plain water) or other medications will lessen the effect of FOSAMAX by decreasing its absorption into the body.

FOSAMAX should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, a FOSAMAX tablet should be swallowed with a full glass of water (6-8 oz). To facilitate gastric emptying FOSAMAX oral solution should be followed by at least 2 oz (a quarter of a cup) of water. Patients should not lie down for at least 30 minutes and until after their first food of the day. FOSAMAX should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal

adverse experiences (see WARNINGS, PRECAUTIONS, *Information for Patients*).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see PRECAUTIONS, *General*).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience.

Treatment of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 70 mg tablet once weekly

  or

- one bottle of 70 mg oral solution once weekly

  or

- one 10 mg tablet once daily

Treatment to increase bone mass in men with osteoporosis

The recommended dosage is:

- one 70 mg tablet once weekly

  or

- one bottle of 70 mg oral solution once weekly

  or

- one 10 mg tablet once daily

Prevention of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 35 mg tablet once weekly

or

- one 5 mg tablet once daily

The safety of treatment and prevention of osteoporosis with FOSAMAX has been studied for up to 7 years.

Treatment of glucocorticoid-induced osteoporosis in men and women

The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women notreceiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

Paget's disease of bone in men and women

The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's disease

In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with FOSAMAX. Specific retreatment data are not available, although responses to FOSAMAX were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with FOSAMAX may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment

may also be considered in those who failed to normalize their serum alkaline phosphatase.

HOW SUPPLIED

No. 3759 – Tablets FOSAMAX, 5 mg, are white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other. They are supplied as follows:

NDC 0006-0925-31 unit-of-use bottles of 30
NDC 0006-0925-58 unit-of-use bottles of 100.

No. 3797 – Tablets FOSAMAX, 10 mg, are white, oval, wax-polished tablets with code MRK on one side and 936 on the other. They are supplied as follows:

NDC 0006-0936-31 unit-of-use bottles of 30
NDC 0006-0936-58 unit-of-use bottles of 100
NDC 0006-0936-28 unit dose packages of 100
NDC 0006-0936-82 bottles of 1,000.

No. 3813 – Tablets FOSAMAX, 35 mg, are white, oval, uncoated tablets with code 77 on one side and a bone image on the other. They are supplied as follows:

NDC 0006-0077-44 unit-of-use blister package of 4
NDC 0006-0077-21 unit dose packages of 20.

No. 8457 – Tablets FOSAMAX, 40 mg, are white, triangular-shaped, uncoated tablets with code MSD 212 on one side and FOSAMAX on the other. They are supplied as follows:

NDC 0006-0212-31 unit-of-use bottles of 30.

No. 3814 – Tablets FOSAMAX, 70 mg, are white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the other. They are supplied as follows:

NDC 0006-0031-44 unit-of-use blister package of4

NDC 0006-0031-21 unit dose packages of 20.

No. 3833 – Oral Solution FOSAMAX, 70 mg, is a clear, colorless solution with a raspberry flavor and is supplied as follows:

NDC 0006-3833-34 unit-of-use cartons of 4 single-dose bottles containing 75 ml each.

Storage

FOSAMAX Tablets:

Store in a well-closed container at room temperature, 15-30°C (59-86°F).

FOSAMAX Oral Solution:

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Do not freeze.

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued Month Year

Printed in USA

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[Exhibit 162 to Ecklund Declaration]

The rationales provided in blue were lifted from our previous submission. Obviously we will need to provide a stronger argument because they did not agree with our last proposal.

USPC: Warnings and Precautions

Merck proposes the following revisions to the FDA proposed labeling. We believe it is essential to inform physicians that the pain syndrome (perceived as thigh or groin pain) indicates the possibility of an incomplete fracture of the proximal femur that a physician needs to evaluate. While many physicians commonly equate the term "stress" fracture with an "incomplete" fracture, the description of a fracture as a stress fracture simply indicates that the fracture —complete or incomplete —was not due to external trauma but caused by one or more high loading episodes that produced a fracture that extended partially (i.e., incomplete) or completely through both cortices of a bone. The objective of the precaution stated in the last paragraph of this section of labeling is to identify incomplete stress fractures before they evolve into a completed femur fracture. Merck believes it is important to make it clear to physicians that there are a number of causes of stress fracture of the proximal femur that may be well known to orthopedic surgeons and metabolic bone disease experts, but not widely known by general

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physicians. Thus it is important to inform the group of physicians who prescribe bisphosphonates that the drugs are only one potential factor involved in the development a stress fracture of the femur. Thus physician should evaluate a patient for concurrent conditions that may have caused or contributed to the stress fracture.

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out a femoral stress

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fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of incomplete stress fracture in the contralateral limb. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors and receive appropriate orthopedic care. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

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FOSAMAX PLUS MG

Ariene Comment: At the meeting I wrote this statement: This is contradictory to what is below? Almost never serious although you may get bone pain. Sometimes severe yes, serious no.

Merck agrees to the Medication Guide format inclusion of the serious side effects noted in Warnings and Precautions in the Physician's Information. Merck believes that it is more accurate to state "may cause serious side effects" as for example, the esophageal problems and bone, joint or muscle pain are common, but severe cases are rare.

FOSAMAX PLUS D may cause serious side effects including:

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1. Esophagus problems
2. Low calcium levels in your blood
3. Bone, joint, or muscle pain

4. Severe jaw bone problems (osteonecrosis)
5. Unusual thigh bone fractures

* * *

Merck proposes the following revisions to the FDA proposed labeling. **Merck** has added information to explain that patients with current hypocalcemia should not take FOSAMAX PLUS D.

1. **Low calcium levels in your blood (hypocalcemia)**
   FOSAMAX PLUS D may lower the calcium levels in your blood. If you have low blood calcium should not take Fosamax Plus D FOSAMAX PLUS D. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:
   - Spasms, twitches, or cramps in your muscles
   - Numbness or tingling in your fingers, toes, or around your mouth

   Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take FOSAMAX PLUS D. Take calcium and vitamin D as your doctor tells you to.

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Deleted: , it may get worse during treatment
Deleted: your low blood calcium must be treated before you take FOSAMAX PLUS D
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Merck proposes the following revisions to the FDA proposed labeling. Merck believes it is important for a patient to tell their doctor about all their dental problems. It is an effective way for patients to provide a complete dental history to their physician, it is critical for physicians to recognize dental problems such as periodontal disease and other risk factors for osteonecrosis. Patients need information regarding the nature of jawbone problems, to give the patient some idea of what adverse experience we are referring to.

4. **Severe jaw bone problems (osteonecrosis).**

Tell your doctor about all of your dental conditions. FOSAMAX PLUS D may cause jawbone problems in some people. Jawbone problems may include infection, and delayed healing after teeth are pulled. Severe jaw bone problems may happen when you take FOSAMAX PLUS D. Your doctor should examine your mouth before you start FOSAMAX PLUS D. Your doctor may tell you to see your dentist before you start FOSAMAX PLUS D. It is important for you to practice good mouth care during treatment with FOSAMAX PLUS D.

Merck proposes to retain the sentence stating "FOSAMAX PLUS D is not for use in premenopausal women." It is inappropriate to give FOSAMAX PLUS D to premenopausal women.

FOSAMAX PLUS D is not for use in premenopausal women.

[redacted]

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Merck proposes to retain some of the overdose labeling Local toxicity is anticipated, not systemic toxicity from high oral doses of the drug. Also, it is important for the patient to know not to vomit or lie down as both situations would increase the potential for esophageal toxicity. Vomiting specifically would increase the risk of aspiration pneumonia. You want to prevent the occurrence of reflux.

If you take too much FOSAMAX PLUS D, call your doctor or go to the nearest hospital emergency room right away. Do not try to vomit. Do not lie down.

Merck proposes to retain the other important potential side effects as shown below.

* * *

[Exhibit 167 to Ecklund Declaration]

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION	**MDL No. 2243** Civil Action No. 08-08(GEB)
THIS DOCUMENT RELATES TO: **DENMAN JONES,** **Plaintiff,** v. **MERCK SHARP & DOHME CORP. f/k/a MERCK & CO., INC.,** **Defendant.**	**Civil Action No.:** **COMPLAINT AND JURY DEMAND**

Plaintiff, DENMAN JONES ("Plaintiff"), by and through his attorneys, WEITZ & LUXENBERG, P.C., for Plaintiff's Complaint against Defendant, MERCK SHARP & DOHME CORP. f/k/a MERCK & CO., INC. ("Merck" or "Defendant"), alleges as follows:

NATURE OF THE CASE

1. This is a civil action for personal injury suffered by Plaintiff, DENMAN JONES against the Defendant, MERCK SHARP & DOHME CORP. f/k/a MERCK & CO., INC., who was responsible for the design, manufacture and sale of the prescription drug, Fosamax, a bone loss preventative medication which was a substantial contributing factor in causing Plaintiff's femur fracture.

* * *

Defendant's Failure to Warn of the Dangers of Fosamax

41. Despite its knowledge of these dangerous side-effects that can result from long-term Fosamax/alendronate use, Defendant refuses to warn patients, physicians and the medical community about the risk of severely suppressed bone turnover. Defendant continues to defend Fosamax, mislead physicians and the public, and minimize unfavorable findings.

42. Defendant knew of the significant risk of severely suppressed bone turnover, brittle bones, and multiple stress fractures that could result from long-term Fosamax use, but did not adequately and sufficiently warn consumers, including Plaintiff, Plaintiff's physician or the medical community of such risks.

43. Defendant, particularly with its heightened knowledge and experience, knew or should have known that long-term use of bisphosphonates, including Fosamax, could inhibit the production of new bone cells (osteoblasts) and therefore, would prevent repair of naturally occurring micro-fractures in the femur which could lead to serious femur fractures, and/or that prolonged suppression of bone remodeling with Fosamax could lead to serious femur fractures, and the femur fractures caused by long-term Fosamax use could occur despite the apparent absence of sufficient trauma.

44. Prior to Plaintiff's suffering from a fracture of his right femur, Defendant received adverse reaction reports regarding numerous Fosamax users throughout the country that these patients were

experiencing bone brittleness, susceptibility to fractures, femoral stress fractures and/or femoral shaft fractures after the long-term use of Fosamax.

45. Defendant has disregarded and has refused to follow-up on the reports of patients, who after using Fosamax, have experienced and reported bone brittleness, susceptibility to fractures, femoral stress fractures and/or femoral shaft fractures.

46. Defendant has failed to submit these reported adverse consequences to the FDA and have failed to advise physicians and the public.

47. Defendant failed to change any of its prescribing information, package inserts or drug manuals supplied to the medical and pharmaceutical professions and the general public in order to warn of the potential for femur fractures after long-term Fosamax use, until finally ordered to do so by the FDA on October 13, 2010.

48. Consumers, including Plaintiff, who have used Fosamax had several alternative safer products available to treat their condition.

49. Adverse Event data maintained by the FDA indicate serious Adverse Events reported in connection to Fosamax, including, femur fractures, severe esophageal adverse reactions requiring hospitalization, musculoskeletal pain, osteonecrosis of the jaw and renal insufficiency.

50. At all relevant times Defendant was responsible for or involved in designing, manufacturing, marketing, advertising, distributing and selling Fosamax.

51. Defendant has marketed their alendronate drugs as effective for the treatment and prevention of osteoporosis in post-menopausal women, to increase bone mass in men with osteoporosis, for the treatment of glucocorticoid induced osteoporosis in men and women and for the treatment of Paget's disease, and that it lacks certain side-effects of other bone loss treatments.

52. Defendant has been warned at least five times by the FDA; three times in 1997, once in 1999, and once in 2001, for misleading the public through use of brochures, Journal Ads, slide presentations, web sites and television advertisements which made false and misleading statements, and overstated the benefits and efficacy of Fosamax, while minimizing the serious risks associated with the drug.

53. Defendant ignored the correlation between the use of Fosamax and the increased risk of developing brittle bones, multiple stress fractures and femur fractures, despite the scientific and medical evidence available.

54. Defendant did not provide adequate warnings to doctors, the health care community and the general public about the increased risk of serious adverse events that are described herein and that have been reported by the medical community.

55. Defendant knowingly withheld or misrepresented information required to be submitted under the FDA's regulations, which information was material and relevant to the harm in question.

56. Defendant expressly warranted that Fosamax was safe and fit for use by consumers, that they were of merchantable quality, that they did not produce

dangerous side-effects, and that they were adequately tested and fit for their intended use, even though they are not safe and have numerous serious side-effects, many of which Defendant did not accurately warn about.

Plaintiff's Use of Fosamax

57. Plaintiff, Denman Jones is a citizen of the United States of America, and is a resident of the City of Grand Junction, in Mesa County in the State of Colorado.

58. Plaintiff, Denman Jones was born on May 6, 1960.

59. Upon information and belief, Plaintiff, Denman Jones was prescribed and began taking Fosamax as prescribed by Plaintiff's physicians, beginning in approximately 2005, and used it until approximately 2008. Fosamax was provided to Plaintiff in a condition that was substantially the same as the condition in which it was manufactured and sold.

60. Plaintiff, Denman Jones used Fosamax as prescribed and in a foreseeable manner.

61. Upon information and belief, on or about November 21, 2008, Plaintiff, Denman Jones suffered a fracture of his right femur.

62. Upon information and belief, as a result of using Defendant's Fosamax, Plaintiff, Denman Jones suffered from a fracture of his right femur, diagnosed on or about November 21, 2008.

63. Upon information and belief, on or about November 21, 2008, Plaintiff, Denman Jones underwent surgery for his right femur fracture at St.

Mary's Hospital & Regional Medical Center in Grand Junction, Colorado.

64. Plaintiff's femur fracture was due to the harmful long-term effects of Fosamax use, a consequence that was never made known to Plaintiff or Plaintiff's physicians by Defendant.

65. Defendant knew or should have known and failed to warn that long-term use of Fosamax was unsafe because it could cause femur fractures of the type that Plaintiff suffered.

66. Plaintiff would not have used Fosamax for so many years had Defendant properly disclosed the risks associated with its long-term use.

67. Defendant knew or should have known, at all times material hereto, that Fosamax was in a defective condition, and was and is inherently dangerous and unsafe when used in the manner instructed and provided by Defendant.

68. As a result of Defendant's actions, Plaintiff and Plaintiff's prescribing physicians were unaware and could not have reasonably known or have learned through reasonable diligence that Plaintiff had been exposed to the risks identified in this complaint, and that those risks were the direct and proximate result of Defendant's acts, omissions and misrepresentations.

69. As a result of taking Fosamax, Plaintiff, Denman Jones suffered compensable injuries, including but not limited to the following:

(a) severe and permanent physical and medical injuries and associated disabilities;

(b) severe past and future pain and suffering;

(c) severe past and future mental anguish;

(d) loss of enjoyment of life

(e) increased risk of health problems;

(f) past and future medical care and monitoring; and

(g) loss of past and future income.

FIRST CLAIM FOR RELIEF:
FAILURE TO WARN
New Jersey Product Liability Act
(N.J.S.A. 2A:58C-1, *et seq.*); and
In the Event
Colorado Failure to Warn Law
is to be Applied

70. Plaintiff realleges and incorporates by reference all other paragraphs of this Complaint as if each were set forth fully and completely herein.

71. Defendant researched, tested, developed, designed, licensed, manufactured, packaged, inspected, labeled, distributed, sold, marketed, promoted and/or introduced Fosamax into the stream of commerce and in the course of same, directly advertised or marketed Fosamax to consumers or persons responsible for consumers, and therefore, had a duty to warn Plaintiff and Plaintiff's physicians of the risk associated with the use of Fosamax, which they know or have reason to know and are inherent in the use of pharmaceutical products.

72. Defendant had a duty to warn of adverse drug reactions, which they know or have reason to know can be caused by the use of Fosamax and/or are associated with the use of Fosamax, including its propensity to cause and/or contribute to femur fractures.

73. Fosamax was under the exclusive control of Defendant and was not accompanied by appropriate warnings regarding all possible adverse side-effects and complications associated with the use of Fosamax, nor with adequate warnings regarding the risk of severely suppressed bone turnover, resulting stress fractures, femur fractures and other severe and permanent injuries associated with its use. The warnings given did not accurately reflect the risk, incidence, symptoms, scope or severity of such injuries to the consumer as compared with other older bone loss treatment medications, which possessed a lower risk of adverse events regarding the comparative severity, duration and extent of the risk of injuries with such use of Fosamax.

74. Defendant downplayed the serious and dangerous side-effects of Fosamax to encourage sales of the product. Consequently, Defendant placed their profits above its customers' safety.

75. Defendant failed to timely and reasonably warn Plaintiff and Plaintiff's prescribing physicians of material facts regarding the comparative safety and efficacy of Fosamax. Fosamax would not likely have been prescribed or used had those facts been made known to such providers and consumers, including Plaintiff.

76. Due to the inadequate warning regarding femur fractures, Fosamax was in a defective condition and unreasonably dangerous at the time that it left the control of the Defendant.

77. Defendant's warnings were overwhelmed, downplayed and otherwise suppressed by Defendant's advertisement campaign, which did not demonstrate

that Fosamax presented multiple and dangerous medical risks, including the risk of suppressed bone turnover resulting in stress fractures and femur fractures.

78. Defendant failed to perform or otherwise facilitate adequate testing. Such testing would have shown that Fosamax posed serious and potential life threatening side-effects and complications with respect to which full and proper warning accurately and fully reflecting the symptoms, scope and severity should have been made to medical care providers, the FDA, and the public, including Plaintiff.

79. Defendant, as a manufacturer of pharmaceutical drugs, is held to the level of knowledge of an expert in the field. Further, Defendant had knowledge of the dangerous risks and side-effects of Fosamax.

80. Plaintiff did not have the same knowledge as Defendant and no adequate warning was communicated to Plaintiff's physicians.

81. Had Plaintiff been adequately warned of the potential serious adverse effects of the Defendant's Fosamax, Plaintiff would not have purchased or taken Fosamax and could have chosen to request other treatments or prescription medications.

82. Upon information and belief, had Plaintiff's prescribing physicians been adequately warned of the potential adverse effects of the Defendant's Fosamax, Plaintiff's prescribing physicians would have discussed risks of femur fractures with Plaintiff and/or would not have prescribed Fosamax

83. Defendant had a continuing duty to warn consumers, including Plaintiff, Plaintiff's physicians

and the medical community of the dangers associated with Fosamax. By negligently and/or wantonly failing to adequately warn of the dangers associated with its use, Defendant breached their duty.

84. As a foreseeable, direct, and proximate result of the aforementioned wrongful acts and omissions of Defendant, Plaintiff was caused to suffer from a fracture of his right femur and endured surgery to repair said fracture, as well as other severe and personal injuries which are permanent and lasting in nature, physical pain, mental anguish and diminished enjoyment of life. Plaintiff has endured and continues to suffer the mental anguish and psychological trauma of living with the knowledge that Plaintiff has suffered these serious and dangerous side-effects.

WHEREFORE, Plaintiff demands judgment against the Defendant individually, jointly and/or severally and demands compensatory, statutory and punitive damages available under applicable law, together with interest, costs of suit, attorneys' fees and all such other relief as the Court deems just and proper.

* * *

[Exhibit 174 to Ecklund Declaration]

To: Daifotis, Anastasia G. <anastasia_daifotis@merck.com>

From: Santora, Arthur C. </O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=SANTORAA>

Cc:

Bcc:

Received Date: 2003-03-04 13:56:47

Subject: FW: My Concerns

Anastasia,

I am happy to do this type of interaction with the thought leaders when they don't have their facts straight (probably been to one to many Lilly hired gun presentations) as I think they are critical to the success of FOSAMAX in Phase V. I think all the MDs in the Bone Group (AKA, CR. Endocrine) share this belief. However, I don't think that this approach is shared in all therapeutic areas. Perhaps that is why FOSAMAX does better than management expects and some other products that don't have full MRL MD support for this type of activity (for one reason or another) don't live up to their potential.

I think that Barry knows "in his heart" how important this type of activity is. But, he also knows that his management hasn't given him the funds to support staff to deal with Phase V issues and that his performance will be rated on the speed and quality of Phase I-III development. You have seen his 2003

objectives -- is there a Clinical Research Phase V support objective on it?

That said, do you think a polite memo to Barry and/or Peter Kim might 1) help get them thinking more about the importance of Clinical Research to a product's Phase V life; 2) not be at all useful ; or 3) get me fired or at least "in trouble"? Given that the memo that I wrote to Ed Scolnick several years ago pointing out that he had given out Divisional Awards to number of other Merck staff for things (FOSAMAX developmental activities) that I had actually done didn't get me fired, I doubt a respectful memo would do so now.

What do you think?

Art

-----Original Message----

From: Nebel, Mark W

Sent: Tuesday, March 04, 2003 6:29 AM

To: Yates, John; Santora, Arthur C.

Cc: Daifotis, Anastasia G.; Orloff, John J; Harris, Michael M. HSA; Neal, Greg J.

Subject: RE: My Concerns

Thank you for the support.

I have asked Mike Harris (HSA) to help coordinate a conference call.

Mark

-----Original Message----

From: Yates, John

Sent: Monday, March 03, 2003 8:39 PM

To: Santora, Arthur C.

Cc: Daifotis, Anastasia G.; Nebel, Mark W; Orloff, John J

Subject: RE: My Concerns

Thanks Art. I know you will be able to convince Gratton with reason. John

-----Original Message----

From: Santora, Arthur C.

Sent: Monday, March 03, 2003 12:22 PM

To: Yates, John

Cc: Daifotis, Anastasia G.; Nebel, Mark W; Orloff, John J

Subject: RE: My Concerns

John,

Anastasia and I will discuss and one of us will discuss this with Dr. Woodson. He has some basic misconceptions about dead bone, pharmacokinetics of bisphosphonates and the like. Why would he think that bone containing alendronate cannot undergo resorption?

Interesting that he is not concerned about raloxifene's (unknown) cardiovascular safety profile. As raloxifene has the same risk of thrombosis and PE as does estrogen, I am going to have to see a lot of safety data to convince me that it would not have the same effect as HRT did in HERS and the WHI.

Art

-----Original Message----

From: Yates, John

Sent: Monday, March 03, 2003 11:26 AM

To: Daifotis, Anastasia G.; Santora, Arthur C.; Nebel, Mark W

Subject: FW: My Concerns

Art and Anastasia

Grattan Woodson copied me on this. I think we should address his concerns directly. The rat medullary remodelling model provides proof that old bone impregnated with ALN can be resorbed. The dog fracture studies also help. Would one of you be willing to follow up?

Thanks

John

-----Original Message-----

From: Grattan Woodson [mailto:gwoodson@mindspring.com]

Sent: Monday, March 03, 2003 12:07 AM

To: Nebel, Mark W

Cc: Harris, Michael M. (HSA); Kotzin, Robin; John_Yates@merck.com

Subject: My Concerns

Hi Mark,

Yes, I am fine. No health or personal problems or anything. I do owe you an explanation though for my decision for suspending my speaking programs for Fosamax.

For a couple of years I have been looking into the bisphosphonate half-life issue. I have found that there is very little data on this area. What is known is that small bisphosphonates like alendronate are retained during bone formation, virtually life-long, in the skeleton in an unaltered state. The 10 year half-life figure in the PI is, in my opinion, an unwarranted estimate that depends on the ability of the bone containing the alendronate being susceptible to osteoclastic resorption. That human bone doped with alendronate can undergo osteoclastic bone resorption is as far as I can tell an unproven assumption. If retained alendronate prevents resorption, old dead bone would be expected to accumulate and become hyper-mineralized and fracture prone. Mircofractures developing in scattered islands of dead bone would

weaken the bone ultimately resulting in clinical fractures.

Under this scenario the fractures would be an iatrogenic complication of therapy. I have been looking for any signs that this scenario developing in my patients since I have been prescribing small bisphosphonates to patients since 1984. Last year, I had two patients who had been on Didronel for several years before beginning alendronate in 1995 suffered vertebral fractures. These are the first such patients I have cared for in years and came as a surprise to me. Of course I realize that fractures are common event in osteoporosis patients even treated ones. While I can not be sure whether of not these patient's fractures were related to my theoretical concern or not, this development has weighed heavily on me for several months. I have also been concerned by the upturn in fractures in the patient treated continuously for 10 years now with alendronate.* My attempts to learn more about the fracture rates in these patients have not proved fruitful. Until I can be convinced of the long-term safety of alendronate, I have decided that it would not be ethical for me to speak on behalf of Fosamax. Certainly this decision will also effect my clinical management of patients however I have not yet thought this through thoroughly.

I have no intention of discussing these speculations with others or spreading unfounded notions about Fosamax. Furthermore, I have no plans to speak for P&GP or Aventis nor will I discuss this communication to them or anyone else. I do plan to continue to speak for Lilly but do not plan to discuss my concerns about small bisphosphonates with them either. My long experience working with MRL and the

sales side of Merck has left no doubt in my mind about your commitment to patient safety and science. I suspect that MRL has been aware of this potential adverse drug side effect of small bisphosphonates and has already given these concerns careful thought. Hopefully then, this concern can be cleared up quickly.

Best regards,

Grattan Woodson, MD

* Lieberman (NEJM 1995), Favus (ASBMR 1997), Tonino (JCE 2000)

----- Original Message -----

From: Nebel, Mark W

To: Grattan Woodson

Sent: Sunday, March 02, 2003 9:27 PM

Subject: RE: 4-10-03, 4-23-03 & 6-6-03 Cancellations

Dr. Woodson,

Is everything ok?

Mark Nebel

Cell 678 427-6312

-----Original Message-----

From: Grattan Woodson
[mailto:gwoodson@mindspring.com]

Sent: Sunday, March 02, 2003 10:18 AM

To: Fortier, Melissa A

Cc: Kotzin, Robin; Nebel, Mark; Harris, Michael M. (HSA)

Subject: 4-10-03, 4-23-03 & 6-6-03 Cancellations

Dear Melissa,

With regret, I have decided to cancel these three Merck programs that were previously scheduled and do not plan to accept any new Merck speaking programs at this time. I am very sorry for the inconvenience these cancellations may cause you and the sales team at Merck who were depending on me to speak for the. Please forgive me and pass on my apologies. I have been a very happy and satisfying experience working with the Fosamax Sales and Scientific Team in the past and hope that my decision to suspend speaking for Merck at this time will not interfere too greatly with my relationship with Merck in the future. My door, ears, and eyes will always be open to my friends and colleagues at Merck.

GW

4-10-03: MESA#1622280 Atlanta

4-23-03 MESA#1618760, Decatur

6-6-03: MESA#1620228 Gainesville, GA

Grattan Woodson, MD, FACP

Osteoporosis Center of Atlanta and
The Atlanta Research Center
2801 North Decatur Road
Suite 375
Decatur, GA 30033
Phone: 404-298-9951
Fax: 404-298-5577

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[Exhibit 12 to Confoy Declaration]

James Adams
Associate Director
Worldwide Regulatory
Affiars

Merck & Co., Inc.
P.O. Box 2000, RY 33-200
Rahway NJ 07065-0900
Tel: 732 594 2552
Fax: 732 594 5235
james_adams@merck.com

July 2, 2009

Scott Monroe, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901 -B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Monroe:

NDA 20-560: FOSAMAX™ Tablets
(Alendronate Sodium)

WITHDRAWAL LETTER

Reference is made to the New Drug Application (NDA) cited above for FOSAMAX™ Tablets, submitted by Merck Research Laboratories (MRL), a division of Merck & Co., Inc. Reference is also made to a 22-May-2009 letter received from FDA regarding NDA 20-560/S-054, NDA 21-575/S-015, and NDA 21-

762/S-008 (originally submitted as prior approval supplements changes to the Precaution section of the Product Circular (PC). Further reference is made to a recent 15-Jun-2009 telephone conversation between Mr. Karl Stiller, FDA, and Mr. James Adams, MRL, in which it was confirmed that the quickest route to update the PC with the text recommended in FDA's 22-May-2009 letter was to (1) withdraw the prior approval supplement submitted on 15-Sep-2008, and (2) submit a Changes Being Effected (CBE) Submission.

With this letter, MRL is withdrawing the supplemental application for NDA 20-560/S-054, NDA 21-575/S-015, and NDA 21-762/S-008. Similar letters are being submitted simultaneously with regard to each of the three NDAs to withdraw their corresponding supplements. A CBE has been submitted that updates the FOSAMAX label with the language in the ADVERSE REACTIONS, Post-Marketing Experience as recommended in the Division's 22-May-09 letter. Merck will also be submitting a request for a Type C meeting to discuss with the Division language to describe low-energy fractures of the proximal femur for inclusion in the Precaution section of the FOSAMAX label.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document — Annex — Granularity Document, and the*

International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification. This submission is being transmitted through the FDA's electronic submission gateway.

A list of reviewers who should be provided access to this electronic submission on their desktops may be obtained from Karl Stiller, Senior Regulatory Project Manager, Division of Reproductive and Urologic Products.

We consider the information included in this submission to be a confidential matter and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to James Adams, (732-594-2552) or, in his absence, to Charlotte B. Merritt (732-594-4060).

Sincerely,

/s/ James Adams
James Adams
Associate Director
Worldwide Regulatory Affairs

James Adams
Associate Director
Worldwide Regulatory
Affiars

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July 2, 2009

Scott Monroe, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901 -B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Monroe:

NDA 20-560: FOSAMAX™ Tablets
(Alendronate Sodium)

SUPPLEMENT – CHANGES BEING EFFECTED

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act and in accordance with 506A(d)(3)(B)(*ii*) of the Food, Drug and Cosmetic Act, we submit, for the Agency's review and approval, a supplement to NDA 20-560.

Reference is made to the New Drug Application (NDA) cited above for FOSAMAX™ Tablets, submitted by Merck Research Laboratories (MRL), a

division of Merck & Co., Inc. Reference is also made to a 22-May-2009 letter received from FDA regarding NDA 20-560/S-054, NDA 21-575/S-015, and NDA 21-762/S-008 (originally submitted on 15-Sep-2008), in which the Agency indicated that it did not approve the proposed changes in the Precaution section of the Product Circular (PC). Further reference is made to a recent 15-Jun-2009 telephone conversation between Mr. Karl Stiller, FDA, and Mr. James Adams, MRL, in which it was confirmed that the quickest route to update the PC with the text recommended in the 22-May-2009 letter was to withdraw the prior approval supplement submitted on 15-Sep-2008, followed by a Changes Being Effected Submission. Final reference is made to the withdrawal letter dated 02-Jul-2009.

Merck believes that further discussion in regard to text for the Precaution section of the label concerning low-energy femoral shaft and subtrochanteric fractures would be beneficial. A Type C meeting request will be submitted in order to discuss this issue in more detail.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the Labeling Section(s) of the approved New Drug Application for FOSAMAX™.

As per FDA Guidance to Industry: *Providing Regulatory Submissions in Electronic Format — Content of Labeling*, the proposed labeling is provided in SPL format. Content of labeling [(201.100(d)(3))] has been included in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html. We understand that this version will be transmitted to the

National Library of Medicine for posting on the DailyMed website.

The Microsoft WORD version of the proposed labeling text is also supplied as PROPOSED.DOC within Section 1.14.1.3 Draft labeling text.

The composed USPC [and USPPI] Final Printed Labeling will be submitted on approximately 30-Jul-2009.

The revised labeling will be used on or before 01-Mar-2010 in all packages sold or distributed from the Company's manufacturing facilities.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document — Annex — Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

In accordance with the Prescription Drug User Fee Act of 1992 (PDUFA) and reauthorized in the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the Prescription Drug User Fee Amendments of 2002 (PDUFA III), as indicated in the attached Form 3397, no user fee is required for this supplemental application.

A list of reviewers who should be provided access to this electronic submission on their desktops may be

obtained from Karl Stiller, Senior Regulatory Project Manager, Division of Reproductive and Urologic Products.

We consider the information included in this submission to be a confidential matter and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to James Adams, (732-594-2552) or, in his absence, to Charlotte B. Merritt (732-594-4060).

Sincerely,

/s/ James Adams
James Adams
Associate Director
Worldwide Regulatory Affairs

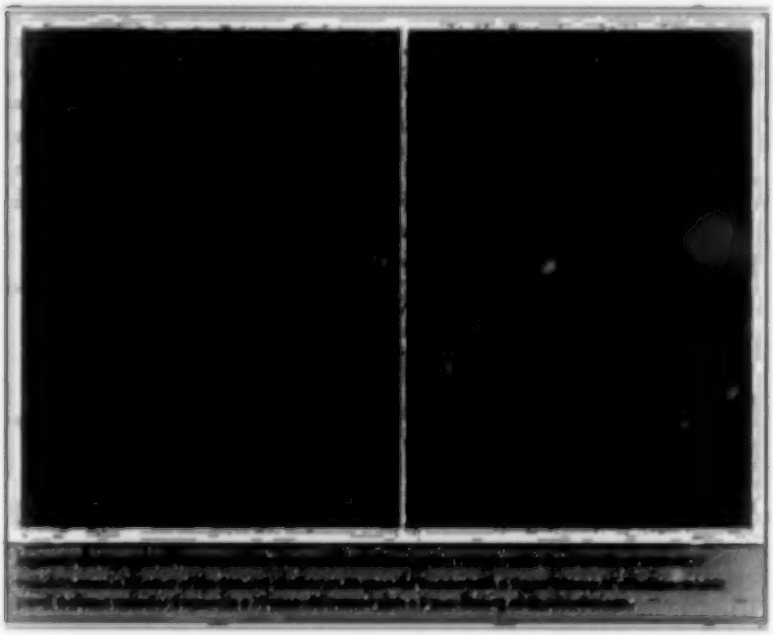
[Exhibit 50 to Confoy Declaration]

Atypical Fractures of the Femoral Diaphysis in Postmenopausal Women Taking Alendronate

TO THE EDITOR: The long-term safety of bisphosphonates for the treatment of osteoporosis has been questioned. Two case series have suggested a link between prolonged bisphosphonate therapy and atypical fractures. In one series, a small number of patients sustained low-energy nonvertebral fractures while receiving long-term alendronate therapy; three were fractures of the femoral shaft.[1] Bone biopsies in these patients showed evidence of severely suppressed bone turnover and fracture healing that was delayed or absent. In the other series, low-energy subtrochanteric fractures were found in nine women who had been receiving long-term alendronate therapy.[2] Theoretically, bisphosphonates suppress bone turnover and thus might be associated with accumulated microdamage in bone. To our knowledge, no study has demonstrated microdamage accumulation in patients treated with bisphosphonates, and data from studies in animals remain difficult to interpret because supranormal doses of bisphosphonates are used. Nevertheless, the possibility that bisphosphonates alter bone strength with prolonged use appears to exist.

We identified 15 postmenopausal women who had been receiving alendronate for a mean (±SD) of 5.4±2.7 years and who presented with atypical low-energy fractures, defined as fractures occurring in a fall from a standing height or less. All patients sustained

subtrochanteric or proximal diaphyseal fractures. Bisphosphonate use was observed in 37% of all patients presenting with low-energy subtrochanteric or diaphyseal fractures. Fractures of the subtrochanteric or diaphyseal regions are relatively rare in postmenopausal women, representing 6% of all osteoporotic hip fractures in our patient population (unpublished data).



Ten of the 15 patients were found to share a unique radiographic pattern, defined as a simple transverse or oblique (≤30°) fracture with beaking of the cortex and diffuse cortical thickening of the proximal femoral shaft. We call this pattern "simple with thick cortices" (Fig. 1). These patients had an average duration of alendronate use of 7.3±1.8 years, which was significantly longer than the duration of 2.8±1.3 years for the five patients without this pattern ($P<0.001$).

Cortical thickening was present in the contralateral femur in all the patients with this pattern. Three of the 15 patients had a history of femoral fractures, all in the contralateral femur, whereas no patients had a history of vertebral fractures. Vitamin D and parathyroid hormone measurements and bone densitometry were not performed during fracture care; therefore, we cannot determine the status of the patients with respect to metabolic bone disease.

Our results provide further evidence of a potential link between alendronate use and low-energy fractures of the femur. In light of the limitations of our study, a prospective study is indicated. Although many possible explanations exist, patients with the unique radiographic pattern shown here may represent a subgroup of the population that is more susceptible to the effects of prolonged suppression of bone turnover. Additional studies are needed to characterize this subgroup and to establish a clear association between atypical fractures of the femur and prolonged bisphosphonate treatment.

Brett A. Lenart, B.S.
Dean G. Lorich, M.D.
Joseph M. Lane, M.D.
Weill Cornell Medical College
New York, NY 10021
lanej@hss.edu

Supported by the Cohn Foundation.

Dr. Lane reports receiving speaking fees from Aventis, GlaxoSmithKline, Eli Lilly, Merck, Novartis, Procter & Gamble, and Roche. No other potential conflict of interest relevant to this letter was reported.

[Exhibit 53 to Confoy Declaration]

To:	Adams, James H (WAG) <james_adams@merck.com>
From:	Marchick, Julie <Julie.Marchick@fda.hhs.gov>
Cc:	
Bcc:	
Received Date:	2008-06-24 18:09:41
Subject:	RE: Fosamax Information Request - Atypical Fractures

Hi Jim,

All case reports of hip and femur fractures should be submitted. We also ask that you further define the fracture site location, if possible. It would be helpful if you classify the fractures based on the location, as follows:

For hip fracture:
intracapsular (neck and head of femur, inside the capsule)
intertrochanteric
subtrochanteric

For femur fracture:
proximal femur (likely will fall into one of the above hip fracture categories)
femoral shaft
supracondylar

We ask that you submit all case reports, from clinical trials and from postmarketing experience.

Thanks,

Julie

From: Adams, James H (WAG)
[mailto:james_adams@merck.com]

Sent: Monday, June 16, 2008 2:36 PM

To: Marchick, Julie

Subject: RE: Fosamax Information Request - Atypical Fractures

Hi Julie,

Could you please clarify that the request includes hip fractures (i.e., hip neck and intertrochanteric) as well as other femoral fractures (sub-trochanteric and fractures lower in the femur) since the references are specific to femoral shaft and subtrochanteric fractures. Thank you.

Best regards,

Jim

From: Marchick, Julie
[mailto:Julie.Marchick@fda.hhs.gov]

Sent: Friday, June 13, 2008 12:24 PM

To: Adams, James H (WAG)

Subject: Fosamax Information Request - Atypical Fractures

Jim,

We are aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates (1–5). The subtrochanteric type of hip or femoral fracture is reportedly rare in patients with osteoporosis not on bisphosphonates. We are concerned about this developing safety signal. Please submit any investigations that you have conducted regarding the occurrence of atypical fractures with bisphosphonate use as well as any investigational plans. Please submit all hip and femoral fracture case reports you have received. Where possible, efforts should be made to clarify the fracture location and the duration of bisphosphonate exposure for all case reports.

We request a written response by Friday, July 11, 2008.

Please contact me if you have any questions.

Thanks,

Julie

Julie Marchick
Regulatory Project Manager

Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.marchick@fda.hhs.gov

References:

1) Neviaser AS, et. al. Low-energy femoral shaft fractures associated with alendronate use. J Orthop Trauma. 2008; 22:346–350.

2) Goh SK, et. al. Subtrochanteric insufficiency fractures in patients on alendronate therapy: A caution. J Bone Joint Surg Br. 2007; 89:349–353.

3) Odvina CV, et. al. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 2005; 90: 1294–1301.

4) Lee P, van der Wall H, Seibel MJ. Looking beyond low bone mineral density: Multiple insufficiency fractures in a woman with post-menopausal osteoporosis on alendronate therapy. J Endocrinol Invest 2007; 30:590–597.

5) Visekruna M, Wilson D, McKiernan FE. Severely suppressed bone turnover and atypical skeletal fragility. J Clin Endocrinol Metab. 2008 epublished ahead of print 6/3/2008.

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[Exhibit 59 to Confoy Declaration]

James Adams
Associate Director
Worldwide
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Rahway NJ 07085-0900
Tel: 732 594 2552
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james_adams@merck.com

September 15, 2008

Mary Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research Division of
Metabolism and Endocrinology Products
590 J -B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 20-560: FOSAMAX™ Tablets
(Alendronate Sodium)

Prior Approval Supplement

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act, we submit, for the Agency's review and approval, a supplement to NDA 20-560.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the

Labeling Section of the approved New Drug Application for FOSAMAX.

Merck is proposing to add language to both the Precaution and Adverse Reaction/ Post-Marketing Experience section of the label to describe low-energy fractures that have been reported, of which some have been stress/ insufficiency, at the subtrochanteric region of the femoral shaft. While these fractures are less common than other osteoporotic low-energy fractures, they occur in a similar population of elderly individuals and have been reported prior to the availability of bisphosphonates. It is not possible with the present data to establish whether treatment with alendronate increases the risk of low-energy subtrochanteric and/or proximal femoral shaft fractures. Nevertheless, considering the clinical importance of these fractures in patients with osteoporosis and their temporal association with bisphosphonate use, the Company believes that it is important to include an appropriate statement about them in the product label. This may further increase physicians' awareness of possible fractures in some osteoporotic patients at risk and allow early intervention, thereby possibly preventing the progression to complete fracture and/or other complications.

As per FDA Guidance to Industry: *Providing Regulatory Submissions in Electronic – Format Content of Labeling*, the proposed labeling is provided in SPL format. Content of labeling [(201.100(d)(3)] has been included in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html.

The Microsoft WORD version of the proposed labeling text is also supplied as PROPOSED DOC within Section 1.14.13 Draft labeling text.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy. Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

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We consider the filing of this supplemental New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to James Adams, (732-594-2552) or, in his absence, to Charlotte B. Merritt (732-594-4060).

Sincerely,

/s/ James Adams
James Adams
Associate Director
Worldwide Regulatory
Affairs

CURRENT CIRCULAR SHOWING REVISIONS

MERCK & CO., INC.

Whitehouse Station, NJ 08889, USA

FOSAMAX®

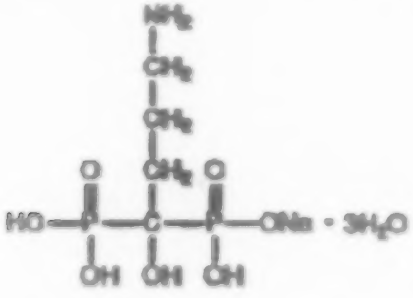
(ALENDRONATE SODIUM) TABLETS AND ORAL SOLUTION

DESCRIPTION

FOSAMAX® (alendronate sodium) is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

The empirical formula of alendronate sodium is $C_4H_{12}NNO_7P_2 \bullet 3H_2O$ and its formula weight is 325.12. The structural formula is:



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COMMENTS/SUPPORT

KEY TO ANNOTATIONS

Sec. 2.5 = Clinical Overview

Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Tablets FOSAMAX for oral administration contain 6. 53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. Tablets FOSAMAX 10 mg also contain carnauba wax.

Each bottle of the oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid. Each bottle also contains the following inactive ingredients: sodium citrate dihydrate and citric acid anhydrous as buffering agents, sodium saccharin, artificial raspberry flavor, and purified water. Added as preservatives are sodium propylparaben 0.0225% and sodium butylparaben 0.0075%.

CLINICAL PHARMACOLOGY

Mechanism of Action

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption.

Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [^{3}H]alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While incorporated in bone matrix, alendronate is not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

Pharmacokinetics

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg tablet in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

FOSAMAX 70 mg oral solution and FOSAMAX 70 mg tablet are equally bioavailable.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49

postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Distribution

Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrators of drug in plasma following therapeutic oral doses are too low (less than 5 ng/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

Metabolism

There is no evidence that alendronate is metabolized in animals or humans.

Excretion

Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a

single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min (64, 78; 90% confidence interval [CI]), and systemic clearance did not exceed 200 mL/min, Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with FOSAMAX (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations

Pediatric: The oral bioavailability in children was similar to that observed in adults; however, FOSAMAX is not indicated for use in children (see PRECAUTIONS, Pediatric Use).

Gender: Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Geriatric: Bioavailability and disposition (urinary excretion) were similar in elderly and younger patients. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is

available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). **FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience with alendronate in renal failure.**

Hepatic Insufficiency: As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.

Drug Interactions (also see PRECAUTIONS, *Drug Interactions*)

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Products containing calcium and other multivalent rations are likely to interfere with absorption of alendronate.

Pharmacodynamics

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Osteoporosis in postmenopausal women

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral (spinal) fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to age 90, the risk of hip fracture in white women increases 50-fold and the risk of vertebral fracture 15- to 30-fold. It is estimated that approximately 40% of 50-year-old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent

inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with FOSAMAX 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received FOSAMAX 5 mg/day, The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with FOSAMAX. In osteoporosis treatment studies FOSAMAX 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25 to 30% to reach a plateau after 6 to 12 months. In osteoporosis prevention studies FOSAMAX 5 mg/day decreased osteocalcin and total serum alkaline phosphatase by approximately 40% and 15%, respectively. Similar reductions in the rate of bone turnover were observed in postmenopausal women during one-year studies with once weekly FOSAMAX 70 mg for the treatment of osteoporosis and once weekly FOSAMAX 35 mg for

the prevention of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with FOSAMAX. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of FOSAMAX 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment; however, serum phosphate returned toward prestudy levels during years three through five. Similar reductions were observed with FOSAMAX 5 mg/day. In one-year studies with once weekly FOSAMAX 35 and 70 mg, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to FOSAMAX but also a decrease in renal phosphate reabsorption.

Osteoporosis in men

Treatment of men with osteoporosis with FOSAMAX 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a one-year study in men with osteoporosis receiving once weekly FOSAMAX 70 mg.

Glucocorticoid-induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs both in males and females of all ages. Osteoporosis occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of up to two years' duration, FOSAMAX 5 and 10 mg/day reduced cross-linked N-telopeptides of type I collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 15 to 30% and 8 to 18%, respectively. As a result of inhibition or bone resorption, FOSAMAX 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1 to 2%) and serum phosphate (approximately 1 to 8%).

Paget's disease of bone

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical

index of disease activity, provides an objective measure of disease severity and response to therapy.

FOSAMAX decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, FOSAMAX 40 mg once daily for six months produced significant decreases in serum alkaline phosphatase as well as in urinary markers of bone collagen degradation. As a result of the inhibition of bone resorption, FOSAMAX induced generally mild, transient, and asymptomatic decreases in serum calcium and phosphate.

Clinical Studies

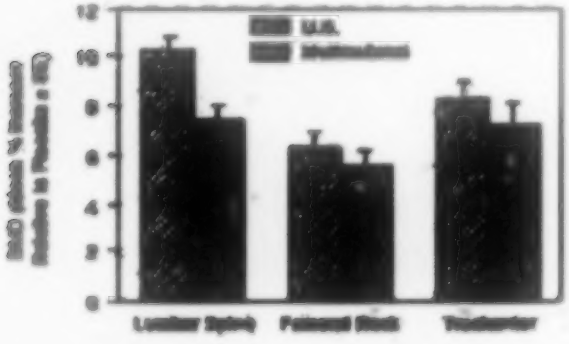
Treatment of osteoporosis

Postmenopausal women

Effect on bone mineral density

The efficacy of FOSAMAX 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration. These included two three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 10 mg/day relative to placebo-treated patients at three years for each of these studies.

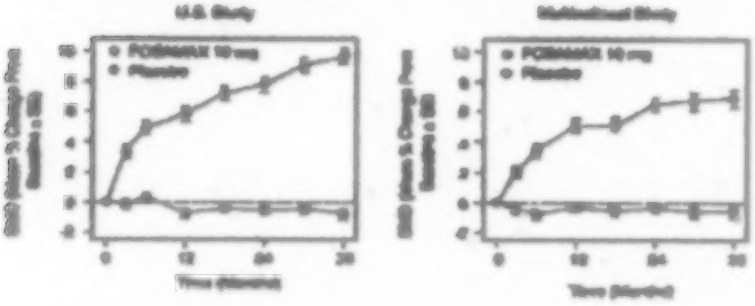
Osteoporosis Treatment Studies in
Postmenopausal Women
Increase in BMD
FOSAMAX 10 mg/day at Three Years



At three years significant increases in BMD, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received FOSAMAX 10 mg/day. Total body BMD also increased significantly in each study, suggesting that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the three years of treatment. (See figures below for lumbar spine results.) In the two-year extension of these studies, treatment of 147 patients with FOSAMAX 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total body were maintained. FOSAMAX was similarly effective regardless of age, race, baseline rate of bone turnover, and baseline BMD in the range studied (at least 2

standard deviations below the premenopausal mean). Thus, overall FOSAMAX reverses the loss of bone mineral density, a central factor in the progression of osteoporosis.

Osteoporosis Treatment Studies in
Postmenopausal Women
Time Course of Effect of FOSAMAX 10 mg/day
Versus Placebo:
Lumbar Spine BMD Percent Change From Baseline



In patients with postmenopausal osteoporosis treated with FOSAMAX 10 mg/day for one or two years, the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those of the placebo groups. These data indicate that continued treatment with FOSAMAX is required to maintain the effect of the drug.

The therapeutic equivalence of once weekly FOSAMAX 70 mg (n=519) and FOSAMAX 10 mg daily (n=370) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the

70-mg once-weekly group (n=440) and 5.4% (5.0, 5.8%; 95% CI) in the 10-mg daily group (n=330). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Effect on fracture incidence

Data on the effects of FOSAMAX on fracture incidence are derived from three clinical studies: 1) U.S. and Multinational combined: a study of patients with a BMD T-score at or below minus 2.5 with or without a prior vertebral fracture, 2) Three-Year Study of the Fracture Intervention Trial (FIT): a study of patients with at least one baseline vertebral fracture, and 3) Four-Year Study of FIT: a study of patients with low bone mass but without a baseline vertebral fracture.

To assess the effects of FOSAMAX on the incidence of vertebral fractures (detected by digitized radiography; approximately one third of these were clinically symptomatic), the U.S. and Multinational studies were combined in an analysis that compared placebo to the pooled dosage groups of FOSAMAX (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a statistically significant reduction in the proportion of patients treated with FOSAMAX experiencing one or more new vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%; a 48% relative risk reduction). A reduction in the total number of new vertebral fractures (4.2 vs. 11.3 per 100 patients) was also observed. In the pooled analysis, patients who received FOSAMAX had a loss in stature that was

statistically significantly less than was observed in those who received placebo (-3.0 mm vs. -4.6 mm).

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline radiographic vertebral fracture and the Four-Year Study of patients with low bone mass but without a baseline vertebral fracture. In both studies of FIT, 96% of randomized patients completed the studies (i.e., had a closeout visit at the scheduled end of the study): approximately 80% of patients were still taking study medication upon completion.

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 2027-patient study (FOSAMAX, n=1022; placebo, n=1005) demonstrated that treatment with FOSAMAX resulted in statistically significant reductions in fracture incidence at three years as shown in the table below.

Effect of FOSAMAX on Fracture Incidence in the Three-Year Study of FIT
(patients with vertebral fracture at baseline)

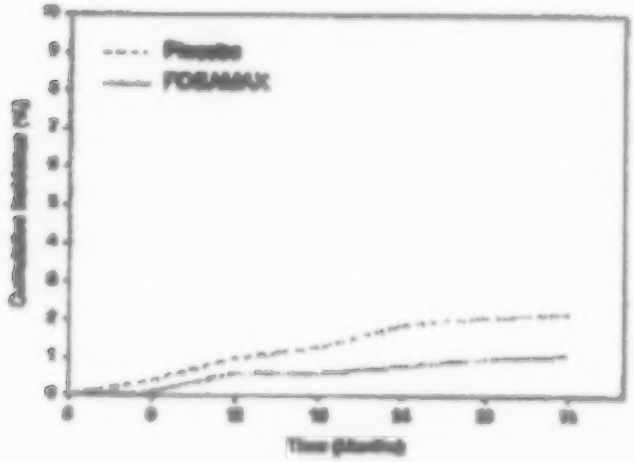
	Percent of Patients			
	FOSAMAX (n=1022)	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk □
Patients with:				
Vertebral fractures (diagnosed by X-ray)[□]				
≥ 1 new vertebral fracture	7.9	15.0	7.1	47□□□
≥ 2 new vertebral fractures	0.5	4.9	4.4	90□□□
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	13.8	18.1	4.3	26[□]
≥ 1 clinical (symptomatic) vertebral fracture	2.3	5.0	2.7	54□□
Hip fracture	1.1	2.2	1.1	51□
Wrist (forearm) fracture	2.2	4.1	1.9	48□

[□]Number evaluable for vertebral fractures: FOSAMAX, n=984; placebo, n=966
□p<0.05, □□p<0.01, □□□p<0.001, [□]p=0.007

Furthermore, in this population of patients with baseline vertebral fracture, treatment with FOSAMAX significantly reduced the incidence of hospitalizations (25.0% v. 30.7%).

In the Three-Year Study of FIT, fractures of the hip occurred in 22 (2 2%) of 1005 patients on placebo and 11 (1.1%) of 1022 patients on FOSAMAX, p=0.047. The figure below displays the cumulative incidence of hip fractures in this study.

Cumulative Incidence of Hip Fractures in the Three-Year Study of FIT
(patients with radiographic vertebral fracture at baseline)



Fracture Intervention Trial: Four-Year Study (patients with low bone mass but without a baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 4432-patient study (FOSAMAX, n=2214; placebo, n=2218) further investigated the reduction in fracture incidence due to FOSAMAX. The intent of the study

was to recruit women with osteoporosis, defined as a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the table below for the patients with osteoporosis.

Effect of FOSAMAX on Fracture Incidence in Osteoporotic[□] Patients in the Four-Year Study of FIT
(patients without vertebral fracture at baseline)

	Percent of Patients			
	FOSAMAX (n=1545)	Placebo (n=1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk (□)
Patients with:				
Vertebral fractures (diagnosed by X-ray)[□□]				
≥ 1 new vertebral fracture	2.5	4.8	2.3	48□□□
≥ 2 new vertebral fractures	0.1	0.6	0.5	78□
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	12.9	16.2	3.3	22□□
≥ 1 clinical (symptomatic) vertebral fracture	1.0	1.6	0.6	41 (NS)[□□□]
Hip fracture	1.0	1.4	0.4	29 (NS)[□□□]
Wrist (forearm) fracture	3.9	3.8	-0.1	NS[□□□]

[□]Baseline femoral neck BMD at least 2 SD below the mean for young adult women
[□□]Number evaluable for vertebral fractures: FOSAMAX, n=1426; placebo, n=1428
[□□□]Not significant. This study was not powered to detect differences at these sites.
□p=0.035, □□p=0.01, □□□p<0.001

Fracture results across studies

In the Three-Year Study of FIT, FOSAMAX reduced the percentage of women experiencing at least one new radiographic vertebral fracture from 15.0% to 7.9% (47% relative risk reduction, $p<0.001$); in the Four-Year Study of FIT, the percentage was reduced from 3.8% to 2.1% (44% relative risk reduction, $p=0.001$); and in the combined U.S./Multinational studies, from 6.2% to 3.2% (48% relative risk reduction, $p=0.034$).

FOSAMAX reduced the percentage of women experiencing multiple (two or more) new vertebral fractures from 4.2% to 0.6% (87% relative risk reduction, $p<0.001$) in the combined U.S./Multinational studies and from 4.9% to 0.5% (90% relative risk reduction, $p<0.001$) in the Three-Year Study of FIT. In the Four-Year Study of FIT, FOSAMAX reduced the percentage of osteoporotic women experiencing multiple vertebral fractures from 0.6% to 0.1% (78% relative risk reduction, $P=0.035$).

Thus, FOSAMAX reduced the incidence of radiographic vertebral fractures in osteoporotic women whether or not they had a previous radiographic vertebral fracture.

FOSAMAX, over a three- or four-year period, was associated with statistically significant reductions in loss of height vs. placebo in patients with and without baseline radiographic vertebral fractures. At the end of the FIT studies the between-treatment group differences were 3.2 mm in the Three-Year Study and 1.3 mm in the Four-Year Study.

Bone histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with FOSAMAX at doses ranging

from 1 to 20 mg/day for one, two, or three years revealed normal mineralization and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal tone histology and increased bone strength observed in rats and baboons exposed to long-term alendronate treatment, support the conclusion that bone formed curing therapy with FOSAMAX is of normal quality.

Men

The efficacy of FOSAMAX in men with hypogonadal or idiopathic osteoporosis was demonstrated in two clinical studies.

A two-year, double-blind, placebo-controlled, multicenter study of FOSAMAX 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). All patients in the trial had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, or 2) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At two years, the mean increases relative to placebo in BMD in men receiving FOSAMAX 10 mg/day were significant at the following sites: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Treatment with FOSAMAX also reduced height loss (FOSAMAX, -0.6 mm vs. placebo, -2.4 mm).

A one-year, double-blind, placebo-controlled, multicenter study of once weekly FOSAMAX 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, 2) a BMD T-score ≤-2 at the lumbar spine and ≤-1 at the femoral neck, or 3) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the

femoral neck. Alone year, the mean increases relative to placebo in BMD in men receiving FOSAMAX 70 mg once weekly were significant at the following sites: lumbar spine, 2.8%; femoral neck, 1.9%; trochanter, 2.0%; and total body, 1.2%. These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.

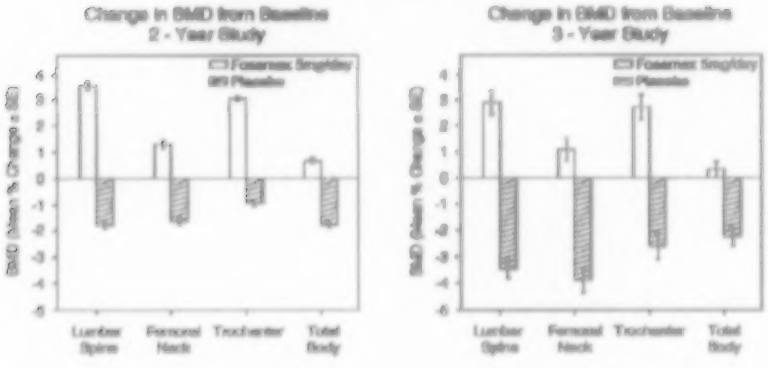
In both studies, BMD responses were similar regardless of age (≥65 years vs. <65 years), gonadal function (baseline testosterone <9 ng/dl vs. 29 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score ≤-2. 5 vs. >-2. 5).

Prevention of osteoporosis in postmenopausal women

Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal women 40–60 years of age. One thousand six hundred nine patients (FOSAMAX 5 mg/day; n=498) who were at least six months postmenopausal were entered into a two-year study without regard to their baseline BMD. In the other study, 447 patients (FOSAMAX 5 mg/day: n=88), who were between six months and three years post menopause, were treated for up to three years. In the placebo-treated patients BMD losses of approximately 1% per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, FOSAMAX 5 mg/day prevented bone loss in the majority of patients and induced significant increases in mean bone mass at each of these sites (see figures below). In addition, FOSAMAX 5 mg/day reduced the rate of bone loss at the forearm by approximately half relative to placebo. FOSAMAX 5 mg/day was similarly effective in this population regard less of age, time

since menopause, race and baseline rate of bone turnover.

Osteoporosis Prevention Studies in Postmenopausal Women



The therapeutic equivalence of once weekly FOSAMAX 35 mg (n=362) and FOSAMAX 5 mg daily (n=361) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women without osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 2.9% (2.6, 3.2%; 95% CI) in the 35-mg once-weekly group (n=307) and 3.2% (2.9, 3.5%; 95% CI) in the 5-mg daily group (n=298). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Bone histology

Bone histology was normal in the 28 patients biopsied at the end of three years who received FOSAMAX at doses of up to 10 mg/day.

Concomitant use with estrogen/hormone replacement therapy (HRT)

The effects on BMD of treatment with FOSAMAX 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomized postmenopausal osteoporotic women (n=425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either estrogen or FOSAMAX alone (both 6.0%).

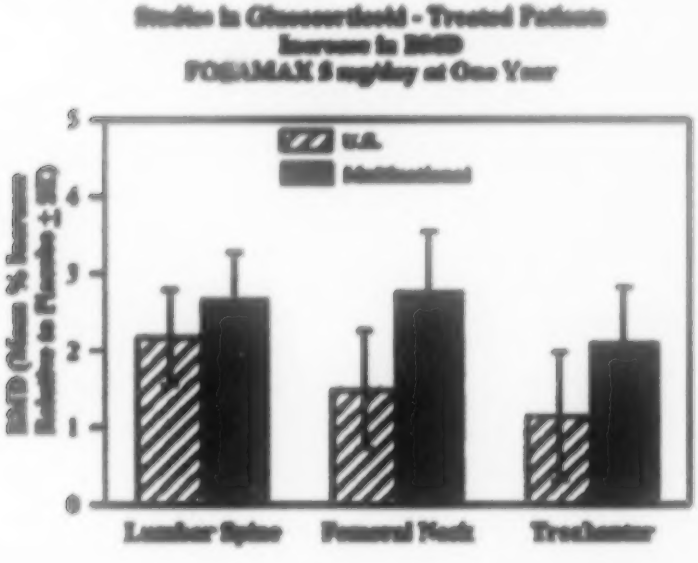
The effects on BMD when FOSAMAX was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo- controlled study in postmenopausal osteoporotic women (n=428). The addition of FOSAMAX 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favorable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD.

Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with FOSAMAX and HRT, 94% on FOSAMAX alone, and 78% on HRT alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence and fracture healing have not been studied.

Glucocorticoid-induced osteoporosis

The efficacy of FOSAMAX 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7. 5 mg/day of prednisone or equivalent) was demonstrated in two, one-year, double-blind, randomized, place controlled, multicenter studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational [which also included FOSAMAX 2.5 mg/day). These studies enrolled 232 and 328 patients, respectively, between the ages of 17 and 83 with a variety of glucocorticoid-requiring diseases. Patients received supplemental calcium and vitamin D. The following figure shows the mean increases relative to placebo in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 5 mg/day for each study.



After one year, significant increases relative to placebo in BMD were seen in the combined studies at

each of these sites in patients who received FOSAMAX 5 mg/day. In the placebo-treated patients, a significant decrease in BMD occurred at the femoral neck (-1.2%), and smaller decreases were seen at the lumbar spine and trochanter. Total body BMD was maintained with FOSAMAX 5 mg/day. The increases in BMD with FOSAMAX 10 mg/day were similar to those with FOSAMAX 5 mg/day in all patients except for postmenopausal women not receiving estrogen therapy. In these women, the increases (relative to placebo) with FOSAMAX 10 mg/day were greater than those with FOSAMAX 5 mg/day at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. FOSAMAX was effective regardless of dose or duration of glucocorticoid use. In addition, FOSAMAX was similarly effective regardless of age (<65 vs. ≥65 years), race (Caucasian vs. other races), gender, underlying disease, baseline BMD, baseline bone turnover, and use with a variety of common medications.

Bone histology was normal in the 49 patients biopsied at the end of the year who received FOSAMAX at doses of up to 10 mg/day.

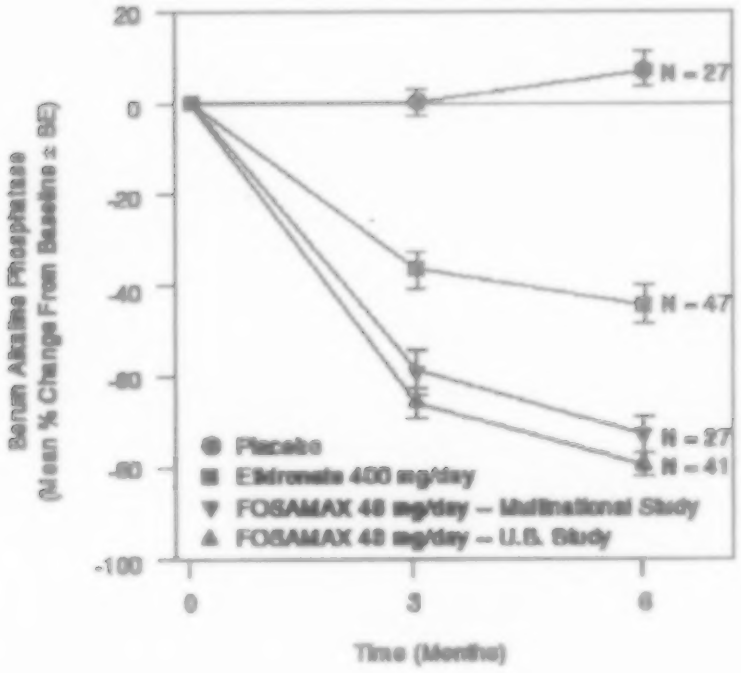
Of the original 560 patients in these studies, 208 patients who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year double-blind extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with FOSAMAX 5 and 10 mg/day, respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.

After one year, 2.3% of patients treated with FOSAMAX 5 or 10 mg/day (pooled) vs. 3.7% of those treated with placebo experienced a new vertebral fracture (not significant). However, in the population studied for two years, treatment with FOSAMAX (pooled dosage groups: 5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) significantly reduced the incidence of patients with a new vertebral fracture (FOSAMAX 0.7% vs. placebo 6.8%).

Paget's disease of bone

The efficacy of FOSAMAX 40 mg once daily for six months was demonstrated in two double-blind clinical studies of male and female patients with moderate to severe Paget's disease (alkaline phosphatase at least twice the upper limit of normal): a placebo-controlled, multinational study and a U.S. comparative study with etidronate disodium 400 mg/day. The following figure shows the mean percent changes from baseline in serum alkaline phosphatase for up to six months of randomized treatment.

Studies in Paget's Disease of Bone
Effect on Serum Alkaline Phosphatase of FOSAMAX 40 mg/day Versus Placebo or Elidronate 400 mg/day



At six months the suppression in alkaline phosphatase in patients treated with FOSAMAX was significantly greater than that achieved with etidronate and contrasted with the complete lack of response in placebo-treated patients. Response (defined as either normalization of serum alkaline phosphatase or decrease from baseline ≥60%) occurred in approximately 85% of patients treated with FOSAMAX in the combined studies vs. 30% in the etidronate group and 0% in the placebo group.

FOSAMAX was similarly effective regardless of age, gender, race, prior use of other bisphosphonates, or baseline alkaline phosphatase within the range studied (at least twice the upper limit of normal).

Bone histology was evaluated in 33 patients with Paget's disease treated with FOSAMAX 40 mg/day for 6 months. As in patients treated for osteoporosis (see *Clinical Studies, Treatment of osteoporosis in postmenopausal women, Bone histology*), FOSAMAX did not impair mineralization, and the expected decrease in the rate of bone turnover was observed. Normal lamellar bone was produced during treatment with FOSAMAX, even where preexisting bone was woven and disorganized. Overall, bone histology data support the conclusion that bone formed curing treatment with FOSAMAX is of normal quality.

ANIMAL PHARMACOLOGY

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

INDICATIONS AND USAGE

FOSAMAX is indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women

- For the treatment of osteoporosis, FOSAMAX increases bone mass and reduces the incidence of fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics.*)

- For the prevention of osteoporosis, FOSAMAX may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture.

  Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be Important when considering the use of FOSAMAX for prevention of osteoporosis.

- Treatment to increase bone mass in men with osteoporosis
- Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density (see PRECAUTIONS, *Glucocorticoid-induced osteoporosis*). Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.
- Treatment of Paget's disease of bone in men and women
  - Treatment is indicated in patients with Paget's disease of bone having alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes
- Patients at increased risk of aspiration should not receive FOSAMAX oral solution
- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, *General*)

WARNINGS

FOSAMAX, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with FOSAMAX. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to in greater in patients who lie down after taking FOSAMAX and/or who fail to swallow it with the recommended amount of water, and/or who continue to take FOSAMAX after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to mental disability, therapy with FOSAMAX should be used under appropriate supervision.

Because of possible irritant effects of FOSAMAX on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodenitis, or ulcers).

There have been post-marketing reports of gastric and duodenal ulcers, some severe and with

complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

General

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FOSAMAX.

Presumably due to the effects of FOSAMAX on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Musculoskeletal Pain

In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). This category of drugs includes

FOSAMAX (alendronate). Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups.

Dental

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., pre-existing dental disease, anemia, coagulopathy, infection).

Patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy should receive care by an oral surgeon. Dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ. Clinical judgment of the treating physician should guide the management plan

or each patient based on individual benefit/risk assessment.

Low-Energy Femoral Shaft Fracture

Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. **[1]** Some patients experienced prodromal pain in the affected area often associated with imaging features of stress fracture weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonate. **[2]** Patients with suspected stress fractures should be evaluated including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse) and receive appropriate orthopedic care. **[3]** Interruption of bisphosphonate therapy in patients with stress fractures **[4]** should be considered pending evaluation of the patient, based on individual benefit/risk assessment. **[3]**

COMMENTS/SUPPORT

1. [Sec. 2.5: p. 5]
2. [Sec. 2.5: p. 7]
3. [Sec. 2.5: p. 5]
4. [Sec. 2.5: p. 8]

Renal insufficiency

FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Glucocorticoid-induced osteoporosis

The risk versus benefit of FOSAMAX for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see INDICATIONS AND USAGE). Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined FOSAMAX and glucocorticoid treatment.

The efficacy of FOSAMAX for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of FOSAMAX has been established in studies of two years duration. The greatest increase in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of FOSAMAX beyond two years has not been studied.

The efficacy of FOSAMAX in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in

postmenopausal women. The efficacy for prevention of non-vertebral fractures has not been demonstrated.

Information for Patients

General

Physicians should instruct their patients to read the patient package insert before starting therapy with FOSAMAX and to reread it each time the prescription is renewed.

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Dosing Instructions

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when it is taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Absorption*).

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of FOSAMAX with a full glass of water (6–8 oz). To facilitate gastric emptying patients should drink at least 2 oz (a quarter of a cup) of water after taking FOSAMAX oral solution. Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet

because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn)they should stop taking FOSAMAX and consult their physician.

Patients should be instructed that if they miss a dose of once weekly FOSAMAX, they should take one dose on the morning after they remember. They should not take two doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.

Drug Interactions
(also see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions)

Estrogen/hormone replacement therapy (HRT)

Concomitant use of HRT (estrogen ± progestin) and FOSAMAX was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence have not been studied (see CLINICAL PHARMACOLOGY, *Clinical Studies,*

Concomitant use with estrogen/hormone replacement therapy (HRT) and ADVERSE REACTIONS, *Clinical Studies, Concomitant use with estrogen/hormone replacement therapy*).

Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of FOSAMAX. Therefore, patients must wait at least one-half hour after taking FOSAMAX before taking any other oral medications.

Aspirin

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of FOSAMAX greater than 10 mg and aspirin-containing products.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

FOSAMAX may be administered to patients taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking FOSAMAX 5 or 10 mg/day compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with FOSAMAX.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3,

and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/ m^2. The relevance of this finding to humans is unknown.

Perafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/ m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Pregnancy

Pregnancy Category C:

Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and

lumbar), skull, and sternebral bones. The above doses ranged from 0.26 limes (1 mg/k) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/cay (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal

harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time poteen cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

There are no studies in pregnant women. FOSAMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSAMAX is administered to nursing women.

Pediatric Use

The efficacy and safety of FOSAMAX were examined in a randomized, double-blind, placebo-controlled two-year study of 139 pediatric patients, aged 4–18 years, with severe osteogenesis imperfecta. One-hundred-and-nine patients were randomized to 5 mg FOSAMAX daily (weight <40 kg) or 10 mg FOSAMAX daily (weight ≥40 kg) and 30 patients to placebo. The mean baseline lumbar spine BMD Z-score of the patients was -4. 5. The mean change in lumbar spine BMD Z-score from baseline to Month 24 was 1. 3 in the FOSAMAX-treated patients and 0.1 in the placebo-treated patients. Treatment with FOSAMAX did not reduce the risk of fracture. Sixteen percent of the FOSAMAX patients who sustained a radiologically-confirmed fracture by Month 12 of the study had delayed fracture healing (callus remodeling)

or fracture non-union when assessed radiographically at Month 24 compared with 9% of the placebo-treated patients. In FOSAMAX-treated patients, bone histomorphometry data obtained at Month 24 demonstrated decreased bone turnover and delayed mineralization time; however, there were no mineralization defects. There were no statistically significant differences between the FOSAMAX and placebo groups in reduction of bone pain.

FOSAMAX is not indicated for use in children.

(For clinical adverse experiences in children, see ADVERSE REACTIONS, *Clinical Studies, Osteogenesis Imperfects.*)

Geriatric Use

Of the patients receiving FOSAMAX in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years of age and 17% (n=550) were ≥75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 45%, 54%, 37%, and 70%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Clinical Studies

In clinical studies of up to five years in duration adverse experiences associated with FOSAMAX

usually were mild, and generally did not require discontinuation of therapy.

FOSAMAX has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of osteoporosis

Postmenopausal women

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: FOSAMAX, 3.2%; placebo, 2.7%. In these study populations, 49–54% had a history of gastrointestinal disorders at baseline and 54–89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX or placebo are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	United States/Multinational Studies		Fracture Intervention Trial	
	FOSAMAX® (n=196)	Placebo (n=397)	FOSAMAX®[1] (n=3736)	Placebo (n=3723)
Gastrointestinal				
abdominal pain	6.6	4.8	1.5	1.5
nausea	3.6	4.0	1.1	1.5
dyspepsia	3.6	3.5	1.1	1.2
constipation	3.1	1.8	0.0	0.2
diarrhea	3.1	1.8	0.6	0.3
flatulence	2.6	0.5	0.2	0.3
acid regurgitation	2.0	4.3	1.1	0.9
esophageal ulcer	1.5	0.0	0.1	0.1
vomiting	1.0	1.5	0.2	0.3
dysphagia	1.0	0.0	0.1	0.1
abdominal distention	1.0	0.8	0.0	0.0
gastritis	0.5	1.3	0.6	0.7
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	4.1	2.5	0.4	0.3
muscle cramp	0.0	1.0	0.2	0.1
Nervous System/Psychiatric				
headache	2.6	1.5	0.2	0.2
dizziness	0.0	1.0	0.0	0.1
Special Senses				
taste perversion	0.5	1.0	0.1	0.0

[1] 10 mg/day for three years
[2] 5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

Rarely, rash and erythema have occurred.

One patient treated with FOSAMAX (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of FOSAMAX in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with FOSAMAX 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 70 mg and FOSAMAX 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related
by the Investigators and Reported in ≥1□ of Patients

	Once Weekly FOSAMAX 70 mg □ (n=519)	FOSAMAX 10 mg/day □ (n=370)
Gastrointestinal		
abdominal pain	3.7	3.0
dyspepsia	2.7	2.2
acid regurgitation	1.9	2.4
nausea	1.9	2.4
abdominal distention	1.0	1.4
constipation	0.8	1.6
flatulence	0.4	1.6
gastritis	0.2	1.1
gastric ulcer	0.0	1.1
Musculoskeletal		
musculoskeletal (bone, muscle, joint) pain	2.9	3.2
muscle cramp	0.2	1.1

Men

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 10 mg/day and a one-year study of once weekly FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for FOSAMAX 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly FOSAMAX 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥2% in patients treated with either FOSAMAX or placebo are presented in the following table.

Osteoporosis Studies in Men
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2% of Patients

	Two-year Study		One-year Study	
	FOSAMAX 10 mg/day (n=146)	Placebo (n=95)	Once Weekly FOSAMAX 70 mg (n=109)	Placebo (n=58)
Gastrointestinal				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.8	0.0
dyspepsia	3.4	0.0	2.8	1.7
diarrhea	1.4	1.1	2.8	0.0
abdominal pain	2.1	1.1	0.9	3.4
nausea	2.1	0.0	0.0	0.0

Prevention of osteoporosis in postmenopausal women

The safety of FOSAMAX 5 mg/day in postmenopausal women 40–60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive FOSAMAX for either two or three years. In these studies the overall safety profiles of FOSAMAX 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with FOSAMAX 5 mg/day and 5.7% of 648 patients treated with placebo.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 35 mg and FOSAMAX 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either once weekly FOSAMAX 35 mg, FOSAMAX 5 mg/day or placebo are presented in the following table.

Osteoporosis Prevention Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1□ of Patients

	Two/Three-Year Studies		One-Year Study	
	FOSAMAX 5 mg/day □ (n=642)	Placebo □ (n=648)	FOSAMAX 5 mg/day □ (n=361)	Once Weekly FOSAMAX 35 mg □ (n=362)
Gastrointestinal				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

Concomitant use with estrogen/hormone replacement therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with FOSAMAX 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Treatment of glucocorticoid-induced osteoporosis

In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX 5 or 10 mg/day or placebo are presented in the following table.

One-Year Studies in Glucocorticoid-Treated Patients
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	FOSAMAX 10 mg/day % (n=157)	FOSAMAX 5 mg/day % (n=161)	Placebo % (n=159)
Gastrointestinal			
abdominal pain	3.2	1.9	0.0
acid regurgitation	2.5	1.9	1.3
constipation	1.3	0.6	0.0
melena	1.3	0.0	0.0
nausea	0.6	1.2	0.6
diarrhea	0.0	0.0	1.3
Nervous System/Psychiatric			
headache	0.6	0.0	1.3

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year.

Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3–12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo.

Osteogenesis Imperfecta

FOSAMAX is not indicated for use in children.

The overall safety profile of FOSAMAX in OI patients treated for up to 24 months was generally similar to that of adults with osteoporosis treated with

FOSAMAX. However, there was an increased occurrence of vomiting in OI patients treated with FOSAMAX compared to placebo. During the 24-month treatment period, vomiting was observed in 32 of 109 (29.4%) patients treated with FOSAMAX and 3 of 30 (10%) patients treated with placebo.

In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of FOSAMAX 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration. These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with an acute-phase response that has been reported in patients receiving bisphosphonates, including FOSAMAX. See ADVERSE REACTIONS, *Post-Marketing Experience, Body as a Whole.*

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8. 0 mg/dL (2.0 mM) and serum phosphate to ≥2.0 mg/dl (0.65 mM) were similar in both treatment groups.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with FOSAMAX, typically in

association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, *Information for Patients*, and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see PRECAUTIONS, *Dental*).

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, *Musculoskeletal Pain*); joint swelling; low-energy femoral shaft fracture (see PRECAUTIONS, *Low-Energy Femoral Shaft Fracture*).

COMMENTS/SUPPORT

Addition of Post-Marketing Adverse Reaction "low-energy femoral shaft fracture," based on the WAES reports listed on paged 37, 38.

Nervous system: dizziness and vertigo.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2), respectively. In males, these values were slightly higher. 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m^2).

No specific information is available on the treatment of overdosage with FOSAMAX. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

FOSAMAX must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only (see PRECAUTIONS, *Information for Patients*). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of FOSAMAX (see PRECAUTIONS, *Drug Interactions*). Waiting less

than 30 minutes, or taking FOSAMAX with food. beverages (other than plain water) or other medications will lessen the effect of FOSAMAX by decreasing its absorption into the body.

FOSAMAX should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, a FOSAMAX tablet should be swallowed with a full glass of water (6–8 oz). To facilitate gastric emptying FOSAMAX oral solution should be followed by at least 2 oz (a quarter of a cup) of water. Patients should not lie down for at least 30 minutes *and* until after their first food of the day. FOSAMAX should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see WARNINGS, PRECAUTIONS, *Information for Patients*).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see PRECAUTIONS, *General*).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience.

Treatment of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 70 mg tablet once weekly

or

- one bottle of 70 mg oral solution once weekly

or

- one 10 mg tablet once daily

Treatment to increase bone mass in men with osteoporosis

The recommended dosage is:

- one 70 mg tablet once weekly

or

- one bottle of 70 mg oral solution once weekly

or

- one 10 mg tablet once daily

Prevention of osteoporosis in postmenopausal woman (*see* INDICATIONS AND USAGE)

The recommended dosage is:

- one 35 mg tablet once weekly

or

- one 5 mg tablet once daily

The safety of treatment and prevention of osteoporosis with FOSAMAX has been studied for up to 7 years.

Treatment of glucocorticoid-induced osteoporosis in men and women

The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

Paget's disease of bone in men and women

The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's disease

In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with FOSAMAX. Specific retreatment data are not available, although responses to FOSAMAX were similar in patents who had received prior bisphosphonate therapy and those who had not. Retreatment with FOSAMAX may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

HOW SUPPLIED

No. 3759 — Tablets FOSAMAX, 5 mg, are white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other. They are supplied as follows:

NDC 0006-0925-31 unit-of-use bottles of 30

NDC 0006-0925-58 unit-of-use bottles of 100

No. 3797 — Tablets FOSAMAX, 10 mg, are white, oval, wax-polished tablets with code MRK on one side and 936 on the other. They are supplied as follows:

NDC 0006-0936-31 unit-of-use bottles of 30

NDC 0006-0936-58 unit-of-use bottles of 100

NDC 0006-0936-28 unit dose packages of 100

NDC 0006-0936-82 bottles of 1,000.

No. 3813 — Tablets **FOSAMAX**, 35 mg, are white, oval, uncoated tablets with code 77 on one side and a bone image on the other. They are supplied as follows:

NDC 0006-0077-44 unit-of-use blister package of 4

NDC 0006-0077-21 unit dose packages of 20.

No. 8457 — Tablets **FOSAMAX**, 40 mg, are white, triangular-shaped, uncoated tablets with code MSD 212 on one side and FOSAMAX on the other. They are supplied as follows:

NDC 0006-0212-31 unit-of-use bottles of 30.

No. 3814 — Tablets **FOSAMAX**, 70 mg, are white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the other. They are supplied as follows:

NDC 0006-0031-44 unit-of-use blister package of 4

NDC 0006-0031-21 unit dose packages of 20.

No. 3833 — Oral Solution **FOSAMAX**, 70 mg, is a clear, colorless solution with a raspberry flavor and is supplied as follows:

NDC 0006-3833-34 unit-of-use cartons of 4 single-dose bottles containing 75 mL each.

Storage

FOSAMAX Tablets:

Store in a well-closed container at room temperature, 15–30°C (59–86°F).

FOSAMAX Oral Solution:

Store at 25°C (77°F), excursions permitted to 15–30°C (59–86°F). [See USP Controlled Room Temperature.) Do not freeze.

Lack-of-efficacy Annual Shelf Expirers
Previously Submitted to FDA*

WWSB Number			
00997273	0402USA00223	0703USA04833	0801SGP00016
00921499	0402USA00297	0703USA04834	0802USA00003
0205USA03318	0405USA00160	0703COL00005	0805USA00009
0205USA02234	0405USA00005	0707PHL00001	0805USA00011
0311USA00004	0810SGP00009	0707PHL00003	0805USA00012
0311USA00041	0810USA00048	0707PHL00004	0805USA00034
0311USA01838	0811SGP00005	0707PHL00005	0804BEL00009
0312USA00476	0812SGP00002	0707SGP00001	0804CHE00016
0403USA00020	0705SGP00005	0709TUR00008	0804CHE00017
0405USA02284	0705SGP00008	0708USA00049	0804USA00007
0405USA01999	0705SGP00007	0708SGP00002	0804USA00008
0411USA00195	0705SGP00006	0708SGP00003	0805SGP00008
0412FRA00007	0705SGP00009	0708SGP00007	0805AUS00019
0412USA00008	0705SGP00010	0708SGP00011	0805USA00011
0505USA01404	0705SGP00011	0708USA00045	0805USA00009
0505AUS00001	0702USA04448	0712HKG00008	0805USA00048
0505USA01835	0705SGP00016	0801SGP00006	0805USA00727
0505USA03125	0703USA03215	0801SGP00009	0805USA00006
0505MYS00005	0703USA03744	0801SGP00010	0805USA00057
0505MYS00006	0703USA03668	0801SGP00011	0805USA03308
0505USA01401	0703USA03669	0801SGP00012	0805USA03310
0505USA02006	0703USA03680	0801SGP00013	0805USA03311
0512USA00304	0703USA03681	0801SGP00014	
0512USA00518	0703USA03682	0801SGP00015	

** Previously submitted to FDA as either "expedited 15-day reports" or as "periodic reports" (pursuant to 21 CFR 314.80 or 21 CFR 600.80).*

Not Previously Submitted to FDA**

WAERS Number			
0610SGP00001	0703SGP00005	0691SGP00001	0804USA01235
0610SGP00002	0703SGP00006	0803USA03222	0804USA01236
0610SGP00003	0703SGP00007	0804USA01287	0804USA01237
0610SGP00006	0703SGP00008	0804USA01288	0804USA01238
0610SGP00007	0703SGP00009	0804USA01289	0804USA01239
0611SGP00007	0703SGP00010	0804USA01290	0807USA00234
0611SGP00008	0703SGP00011	0804USA01291	0807USA00235
0611SGP00010	0709SGP00004	0804USA01292	99073648
0702SGP00012	0709SGP00005	0804USA01293	
0703SGP00003	0710AUS99008	0804USA01294	

*** The reports referenced above have not been previously submitted to FDA and belong to one of the following two categories: reports which meet the criteria for submission to FDA (pursuant to 21 CFR 314.80 or 21 CFR 600.80) and are scheduled for a future "periodic adverse experience report" or as "expedited 15-day report"; or reports which do not meet the criteria for submission to FDA (including non-US non-expedited reports, non-expedited literature reports, initial MedWatch reports received directly from FDA, and initial reports received through the Freedom of Information Act). Reports not previously submitted but meeting criteria for submission will be sent to FDA as either "expedited 15-day reports" or as "periodic reports" with future scheduled "periodic adverse experience report" submissions, as appropriate.*

Patient Information
FOSAMAX® (FOSS-ah-max)
(alendronate sodium) Tablets

Read this information before you start taking FOSAMAX*. Also, read the leaflet each time you refill your prescription, just in case anything has changed. This leaflet does not take the place of discussions with your doctor. You and your doctor should discuss FOSAMAX when you start taking your medicine and at regular checkups.

What is the most important information I should know about FOSAMAX?

- **You must take FOSAMAX exactly as directed to help make sure it works and to help lower the chance of problems in your esophagus (the tube that connects your mouth and stomach). (See "How should I take FOSAMAX?").**

- **If you have chest pain, new or worsening heartburn, or have trouble or pain when you swallow, stop taking FOSAMAX and call your doctor. (See "What are the possible side effects of FOSAMAX?").**

What is FOSAMAX?

FOSAMAX is a prescription medicine for:

- The treatment or prevention of osteoporosis (thinning of bone) in women after menopause. It

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reduces the chance of having a hip or spinal fracture (break).

- Treatment to increase bone mass in men with osteoporosis.
- The treatment of osteoporosis in either men or women who are taking corticosteroid medicines (for example, prednisone).

Improvement in bone density may be observed as early as 3 months after you start taking FOSAMAX even though you won't see or feel a difference. For FOSAMAX to continue to work, you need to keep taking it.

FOSAMAX is not a hormone.

There is more information about osteoporosis at the end of this leaflet.

Who should not take FOSAMAX?

Do not take FOSAMAX if you:

- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes
- Have low levels of calcium in four blood
- Are allergic to FOSAMAX or any of its ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before using FOSAMAX?

Tell your doctor about all of your medical conditions, including if you;

- **have problems with swallowing**
- **have stomach or digestive problems**

- **have kidney problems**
- **are pregnant or planning to become pregnant.** It is not known if FOSAMAX can harm your unborn baby.
- **are breastfeeding.** It is not known if FOSAMAX passes into your milk and if it can harm your baby.

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take FOSAMAX?

- Take 1 FOSAMAX tablet once a day, every day **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take FOSAMAX while you are sitting or standing.
- Swallow your FOSAMAX tablet with a full glass (6-8 oz) of plain water only.

Do **not** take FOSAMAX with:

Mineral water
Coffee or tea
Juice

FOSAMAX works only if taken on an empty stomach.

Do not chew or suck on a tablet of FOSAMAX.

After swallowing your FOSAMAX tablet, wait at least 30 minutes:

- before you lie down. You may sit, stand or walk, and do normal activities like reading.

- before you take your first food or drink except for plain water.
- before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down until after first food of the day.

- It is important that you keep taking FOSAMAX for as long as your doctor says to take it. For FOSAMAX to continue to work, you need to keep taking it.

What should I do if I miss a dose of FOSAMAX or if I take too many?

- If you miss a dose, do not take it later in the day. Continue your usual schedule of 1 tablet once a day the next morning.
- If you think you took more than the prescribed dose of FOSAMAX, drink a full glass of milk and call your doctor right away. Do not try to vomit. Do not lie down.

What should I avoid while taking FOSAMAX?

- Do not eat, drink, or take other medicines or supplements **before** taking FOSAMAX.
- Wait for at least 30 minutes **after** taking FOSAMAX to eat, drink, or take other medicines or supplements.
- Do not lie down for at least 30 minutes **after** taking FOSAMAX. Do not lie down until **after** your first food of the day.

What are the possible side effects of FOSAMAX?

FOSAMAX may cause problems in your esophagus (the tube that connects the mouth

and stomach). (See "What is the most important information I should know about FOSAMAX?".) These problems include irritation, inflammation, or ulcers of the esophagus, which may sometimes bleed. This may occur especially if you do not drink a full glass of water with FOSAMAX or if you lie down in less than 30 minutes or before your first food of the day.

- **Stop taking FOSAMAX and call your doctor right away if you get any of these signs of possible serious problems of the esophagus:**
  - **Chest pain**
  - **New or worsening heartburn**
  - **Trouble or pain when swallowing**
- Esophagus problems may get worse if you continue to take FOSAMAX.
- Mouth sores (ulcers) may occur if the FOSAMAX tablet is chewed or dissolved in the mouth.
- You may get flu-like symptoms typically at the start of treatment with FOSAMAX.
- You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.
- FOSAMAX may cause jaw-bone problems in some people. Jaw-bone problems may include infection, and delayed healing after teeth are pulled.
- The most common side effect is stomach area (abdominal) pain. Less common side effects are nausea, vomiting, a full or bloated feeling in the stomach, constipation, diarrhea, black or bloody stools (bowel movements), gas, eye pain, rash that may be made worse by sunlight, hair loss,

headache, dizziness, a changed sense of taste, joint swelling or swelling in the hands or legs, and bone, muscle, or joint pain.

- **Call your doctor if you develop severe bone, muscle, or joint pain.**
- Patients have experienced fracture in a specific part of the thigh bone. Call your doctor if you develop new or unusual pain in the hip or thigh.

COMMENTS/SUPPORT

Side effect added for consistency with the revision in the USPC.

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the side effects with FOSAMAX. Ask your doctor or pharmacist for more information.

How do I store FOSAMAX?

- Store FOSAMAX at room temperature, 59 to 86°F (15 to 30°C).
- Safely discard FOSAMAX that is out-of-date or no longer needed.
- **Keep FOSAMAX and all medicines out of the reach of children.**

General information about using FOSAMAX safely and effectively

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use FOSAMAX for a condition for which it was not prescribed.

Do not give FOSAMAX to other people, even if they have the same symptoms you have. It may harm them.

FOSAMAX is not indicated for use in children.

This leaflet is a summary of information about FOSAMAX. If you have any questions or concerns about FOSAMAX or osteoporosis, talk to your doctor, pharmacist, or other health care provider. You can ask your doctor or pharmacist for information about FOSAMAX written for health care providers. For more information, call 1-877-408-4699 (toll-free) or visit the following website: www.fosamax.com.

What are the ingredients in FOSAMAX?

FOSAMAX contains alendronate sodium as the active ingredient and the following inactive ingredients:

cellulose, lactose, croscarmellose sodium and magnesium stearate. The 10 mg tablet also contains carnauba wax.

What should I know about osteoporosis?

Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then a similar amount of new bone is formed. This balanced process keeps your skeleton healthy and strong.

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause, and may also occur in men. In osteoporosis, bone is removed faster than it is formed, so overall bone mass is lost and bones become weaker. Therefore, keeping bone mass is important to keep your bones healthy. In both men and women, osteoporosis may also be caused by certain medicines called corticosteroids.

At first, osteoporosis usually has no symptoms, but it can cause fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they can make you shorter. Eventually, your spine can curve and your body can become bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause bones to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of ability to move around (mobility).

Who is at risk for osteoporosis?

Many things put people at risk of osteoporosis. The following people have a higher chance of getting osteoporosis:

Women who:

- Are going through or who are past menopause

Men who:

- Are elderly

People who

- Are white (Caucasian) or oriental (Asian)
- Are thin
- Have family member with osteoporosis
- Do not get enough calcium or vitamin D
- Do not exercise
- Smoke
- Drink alcohol often
- Take bone thinning medicines (like prednisone or other corticosteroids) for a long time

What can I do to help prevent or treat osteoporosis?

In addition to FOSAMAX, your doctor may suggest one or more of the following lifestyle changes:

- **Stop smoking.** Smoking may increase your chance of getting osteoporosis.
- **Reduce the use of alcohol.** Too much alcohol may increase the risk of osteoporosis and injuries that can cause fractures.
- **Exercise regularly.** Like muscles, tones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries, including fractures. Talk with your doctor before you begin any exercise program.
- **Eat a balanced diet.** Having enough calcium in your diet is important. Your doctor can advise you

whether you need to change your diet or take any dietary supplements, such as calcium or vitamin D.

Rx only

* * *

2.5.1 Product Development Rationale

Not applicable

2.5.1 Product Development Rationale

Not applicable

2.5.2 Overview of Biopharmaceutics

Not applicable

2.5.3 Overview of Clinical Pharmacology

Not applicable

2.5.4 Overview of Efficacy

Not applicable

2.5.5 Overview of Safety

The following label change (new text is in italic) is proposed for the alendronate sodium and alendronate sodium/cholecalciferol Company Core Data Sheet (CCDS) under Precautions and Side effects:

Section V. PRECAUTIONS:

Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low and

stress fractures with similar clinical features have also occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g. vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes well tins, chronic alcohol abuse), and receive appropriate orthopedic care, interruption of bisphosphonate therapy in patients with stress fractures should be considered pending evaluation of the patient, based on individual benefit/risk assessment.

Section XL Side Effects

Musculoskeletal: bone, joint, and/or muscle pain, rarely severe and/or incapacitating (see PRECAUTIONS); joint swelling, *low-energy femoral shaft fracture (see PRECAUTIONS).*

This revision is based upon review of spontaneous adverse experience reports from the Merck Worldwide Adverse Experience System (WAES) database. A substantial number of the spontaneous reports are sourced from the literature. A summary of the spontaneous reports follows below.

Introduction

A low-energy fracture is defined as one that is caused by the equivalent of a fall from standing height or less. A stress fracture (also known as an insufficiency fracture) is defined as a partial or complete fracture occurring with either normal or increased activity, but without an identifiable external traumatic event. Stress fractures are included in the larger group of low-energy fractures. Stress fractures arc seen mainly

in postmenopausal osteoporotic women and are becoming more common with the increase of elderly population and its increasing involvement in relatively intensive physical/fitness activities [Ref. 5.4: 6622, 6630, 6634]. Osteoporosis is a systemic skeletal disease and bone is abnormal due to both loss of bone mass and microarchitectural deterioration of the remaining bone. Insufficiency stress fractures are also increasingly recognized in patients with other systemic and localized metabolic conditions including rheumatoid arthritis, systemic lupus erythematosus, osteomalacia, Paget's disease, diabetes mellitus, fibrous dysplasia, pyrophosphate arthropathy, osteogenesis imperfecta, hyperparathyroidism, osteonecrosis, and endogenous or iatrogenic Cushing's syndrome [Ref. 5.4: 6622, 6623, 6626, 6628, 6629, 6630, 6632, 6633]. The proximal femur is one of the most commonly affected sites for insufficiency fractures, as are the pelvis, distal tibia and metatarsals [Ref. 5,4: 6630]. In addition to abnormally decreased bone mineral density (BMD) associated with osteoporosis, long-term immobilization/disuse, and use of glucocorticoids, the presence of joint deformity, leg-length discrepancies, muscle weakness, and spasm with resulting alteration in force distribution across the joints is likely to be very important in the development of insufficiency fractures [Ref. 5. 4: 6627, 6631]. A sudden increase in activity after joint replacement surgery and poor aerobic fitness may also be contributory factors (Ref. 5.4: 6624]. Moreover, some traumatic fractures may have a clinical presentation of a stress fracture as a patient may not tell the physician about a fall (or other external

trauma) that resulted in an incomplete fracture weeks before persistent pain lead to medical evaluation.

Several authors have reported cases of low-energy subtrochanteric/femoral shaft fractures in patients treated with alendronate [Ref 5.4: 5399, 5705, 6175, 6536, 6540, 6605, 6606, 6607, 6608]; of these, 52% were reported to be stress fractures. The published cases listed above have been entered into WAES database and are included in the review below.

Spontaneous reports

Merck & Co., Inc.'s Worldwide Adverse Experience System database was searched for spontaneous reports with a large range of MedDRA preferred terms[1] from healthcare professionals (HCP), including regulatory agencies, in patients treated with alendronate sodium and/or alendronate sodium/cholecalciferol from market introduction (16-Jul-1993 and 10-Mar-2005, respectively) through 30-Jun-2008.

A total of 132 reports [Ref. 5.3.6: 6603] describing low-energy subtrochanteric/mid femoral shaft fractures were identified. Of these, 60% were reported as stress fractures. Forty-six (35%) of the 132 reports were from literature (5 - Odvina et al.; 15 - Lenart, Lane et al; 9 - Goh et al; 9 - Kwek et al; 3 - Visckruna et al; and single case reports by Schneider, Demiralp et al, Cheung et al, Lee et al., and Husada et al) [Ref, 5.4: 5399, 5705, 6175, 6536, 6540, 6568, 6605, 6606, 6607,

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[1] Bone development abnormal, bone formation decreased; fracture delayed union, fracture malunion, fracture nonunion, low turnover osteopathy, pathological fracture, stress fracture, multiple fractures, femur fracture, hip fracture, and femoral neck fracture.

6608], and 24 (52%) of these were identified as stress fractures.

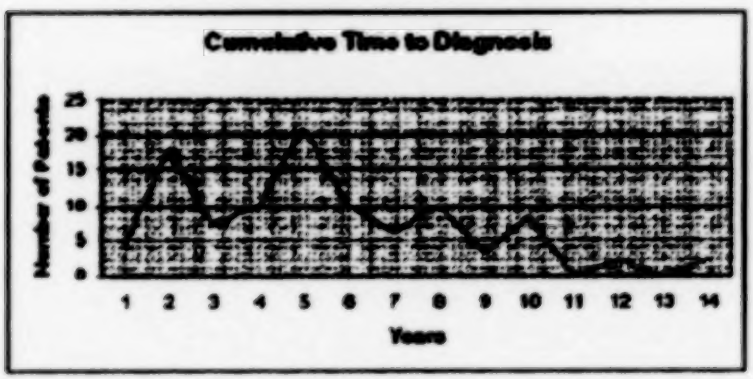
The 132 reports originated from 14 countries with half from the US (n=66, 50%), followed by Singapore (n=45, 34%), and 16% from the remaining 12 countries: Philippines (n-4), Australia (n=4), Malaysia (n=), Japan (n=), Switzerland (n=2), and 1 each from Hong Kong, France, Sweden, Turkey, Colombia, Belgium and Spain. Ninety-seven percent were female patients. he mean and median ages were both 67 years with a range from 37 to 84 years. Sixty-seven percent were aged greater than or equal to 64 years.

In these reports, alendronate therapy was given for the treatment of: osteoporosis (45%), osteopenia (11%), osteoporosis prophylaxis (4%), glucocorticosteriod-induced osteoporosis (4%) and unknown indications (37%). Of note, baseline BMD values were not typically provided to confirm the presence of osteoporosis or otherwise low bone mass prior to initiation of alendronate therapy; in 2 reports (WAES 0606USA00160 and 0610SGP00006) with reported indication of osteoporosis and osteoporosis prophylaxis respectively, the BMD values were within normal limits. The prescribed alendronate dose was not reported in a majority of the reports; however, the weekly 70 mg dose was most commonly used, which is a reflection of the current worldwide distribution pattern. Two patients (WAES 0801SGP00015 and 0804USA020G8) were receiving risedronate – one for 6 years following 4 years therapy with alendronate and the other using alendronate and risedronate concomitantly for 4 years.

The 132 reports were examined for evidence of the time after initiation of treatment with alendronate to the diagnosis of fracture. In 101/132 reports there was sufficient information (either onset and start therapy dates provided or information in the narrative indicating the approximate duration) to estimate the time to diagnosis of fracture after initiation of treatment with alendronate. [Figure 2.5: 1] is a plot of these data. The earliest time was approximately 3 months and the latest time was approximately 14 years [Note: data are presented as reported to the Company]. The mean time to diagnosis was 5.3 years; the median time was 5 years. In one patient (WAES 0709SGP00004), the fracture occurred 1 year after discontinuation of alendronate therapy.

Figure 2.5:1

Cumulative Time to Diagnosis of the Fracture after Starting Treatment With Alendronate



The reports were evaluated for fracture risk factors, including those specifically tied to stress fracture. Seventy of 132 reports (53%) provided information on patient's medical history/concurrent conditions and/or

concomitant medications sufficient to identify stress fracture risk factors[2]. Musculoskeletal disorders, including most commonly osteoarthritis (spine, hip and knee) and rheumatoid arthritis, were reported in 38 of the 70 patients (54%). The presence of joint deformities, muscle imbalance, leg-length discrepancies, and change in activity was common for this subgroup of patients. Other musculoskeletal disorders included systemic lupus erythematosus, hypermobility syndrome; fibromyalgia, myasthenia gravis, mild collagen disorder. Twenty-eight of the 70 patients (40%) had a history of fracture (25% stress fractures, 21% femur fractures; the remaining were vertebral fractures and fractures of bones of the foot), Ten of the 70 patients (14%) sustained subtrochanteric fracture following joint replacement/surgeries. Seventeen patients (24%) had endocrine/metabolic disorders including diabetes mellitus, hypothyroidism and obesity. Use of glucocorticoids was reported in 14 patients (20%) and estrogen therapy in 10 patients (14%). Malignant disease was reported in 10 patients (14%). Three patients (4%) were smokers and 5 patients (7%) had malabsorption due to gastrointestinal disease. In the remaining 47% of the 132 reports there was no information on medical history/concurrent conditions, and/or concomitant therapies precluding evaluation of possible risk factors.

Of the 132 reports of low-energy subtrochanteric/femoral shaft fracture, 80 (60%) were considered as stress/insufficiency fractures based on diagnostic results (e.g., radiographic, and/or bone scan, and/or MRI) or solely clinician's assessment with no

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[2] A patient may have had more than 1 risk factor.

diagnostic verification provided. The remaining 52 (40%) reports did not provide data to allow classification/assessment of the fracture except for 1 report where the fracture was characterized as "spiral with thin cortices".

Prodromal pain in the affected leg mainly on weight-bearing, with duration ranging from 1 week to 2 years, was reported in 48 (36%) of the 132 patients; for the remaining patients this information was not provided. Prodromal pain was reported in 51% (41/80) of the reports of stress fracture. In five of these 41 patients, limited weight bearing led to relief of the pain and healing of the stress fracture in 4 of them.

In this series of 132 reports, radiography was the most frequently used diagnostic method with common findings of cortical thickening localized to the lateral cortex of the proximal femur, periosteal reaction, cortex regeneration, fracture line and callus, described in 43 (54%) of the 80 reports of stress fracture; in very few reports generally thick femoral cortices were noted. Other diagnostic tests that were less frequently reported included bone scintigraphy and MRI with results typically indicating increased bone uptake at the fracture site.

Clinical and laboratory evaluations for known causes of stress fractures (e.g., osteomalacia, collagen disorders, Paget disease, etc.) were described in 21 (16%) of the 132 reports. A mild collagen disorder was suspected in one patient, and Paget disease in another. While bone biopsy results (provided only in 9/132; 7% reports) indicated low bone turnover, no data were presented that indicate that the rate of bone turnover was lower than that typically found during

bisphosphonate therapy. Biochemical markers of bone turnover were within normal range in the reports with this information (14/132; 11%). In two patients, the serum osteocalcin was noted to be low with all other markers within the normal range; the scrum bone-specific alkaline phosphatase was increased in 1 patient and slightly decreased in another. Vitamin D level was within normal limits except for 1 report where it was on the low borderline. It should be noted that generally the clinical and laboratory evaluations were poorly documented often with missing lab and/or reference values.

Based on 65 reports with information on fracture management, the most common treatment was surgical (in 59/65; 91%). Six (9%) patients with incomplete stress fractures were treated conservatively with restricted weight-bearing.

Outcome was reported in less than half of the reports (62/132; 47%). Furthermore, most of the reports with outcome did not provide sufficient data anchor a cl equate follow-up period to allow appropriate evaluation of fracture outcome (e.g., healed fracture, fracture nonunion, fracture delayed union). Review of the fracture outcome in relation to the fracture management and action taken with alendronate therapy is summarized in [Table 2.5:1].

Table 2.5:1

Fracture Outcome Related to Fracture Treatment and Action Taken With Alendronate Therapy

Outcome	Fracture Treatment		Action Taken with Alendronate Therapy	
	Surgical	Non-surgical	Discontinued	Continued
	n=27	n=5	n=28	n=18
Fracture healed	24 (89%)	4 (80%)	25 (89%)	9 (50%)
Fracture not healed	1 (4%)	1 (20%)	1 (4%)	2 (11%)
Unknown	2 (7%)	0 (0%)	2 (7%)	7 (39%)

Comment

In summary, the following features can be noted for the post-marketing reports of low-energy subtrochanteric/femoral shaft fractures:

- Incomplete data in many reports precludes an appropriate assessment;
- The presence of advanced age, female gender, and osteoporosis as well as other important underlying conditions/risk factors are known to predispose the patients to insufficiency fractures and hinder the healing process. The presence of joint deformities, muscle imbalance, leg-length discrepancies, and a change in physical activities was noted in a significant number of patients;
- The duration of alendronate therapy relative to onset of the fracture was 5.3 years mean and 5 years median with a range from 3 months to 14 years;
- A significant number of reports represent published case reports/case series [Ref. 5.4; 5399, 6175, 6568, 6607]; however, little information is available about many of the cases selected by the authors, and inadequate data are available on the

period preceding the start of alendronate treatment; the possibility that other underlying metabolic bone disorders may have been responsible for the fractures, and may have existed prior to the start of alendronate therapy, should also be considered;

- Sixty percent of the 132 low-energy subtrochanteric/femoral shaft fractures were stress (insufficiency) fractures. Fifty-one percent of the stress fracture reports were associated with prodromal leg/hip pain suggestive of incomplete stress fracture;
- In many cases, there was either missing information or inadequate follow-up of the fracture outcome; however, based on the available data, a higher proportion of the fractures were reported to be healing or have healed.
- The data on the outcome relative to action taken with alendronate therapy in response to event are incomplete and do not allow for any conclusions;
- The review of the post-marketing reports describing low-energy subtrochanteric/femoral shaft fractures does not demonstrate a causal link with alendronate therapy.

In conclusion, the spontaneous reports in this review represent low-energy fractures, some described as stress/insufficiency fractures, at the subtrochanteric region of the femoral shaft. While these fractures are less common than other osteoporotic low-energy fractures (representing about 6% of fractures of the femur), they occur in a similar population of elderly individuals and have been reported prior to the availability of bisphosphonates. It is not possible with

the present data to establish whether treatment with alendronate increases the risk of low-energy subtrochanteric and/or proximal femoral shaft fractures. Nevertheless, considering the clinical importance of these fractures in patients with osteoporosis and their temporal association with bisphosphonate use, the Company believes that it is important to include an appropriate statement about them in the product information and precautions needed to identify and manage such fractures. This may further increase physicians' awareness of possible fractures in some osteoporotic patients at risk and allow early intervention thus possibly preventing the progression to complete fracture and/or other complications.

The Company will continue to closely monitor the reports describing low-energy subtrochanteric/femoral shaft fractures and ensure the adequacy of the safety information in the product label.

2.5.6 Benefits and Risks Conclusions

Review of the spontaneous reports of low-energy subtrochanteric femoral fractures supports the proposed label communication under Precautions and Side Effects sections of the CCDS for alendronate sodium and alendronate sodium/cholecalciferol.

Based on the extensive experience with alendronate in patients with osteoporosis of [REDACT] patient-years of treatment, the number of the spontaneous reports of low-energy subtrochanteric/femoral shaft fractures which have been received is very small [REDACT] per 100,000 patient treatment years). The benefit to risk balance for alendronate in the treatment of osteoporosis remains favorable considering that

bisphosphonates reduce the risk of most common hip fractures by approximately 50% in osteoporotic postmenopausal women.

The MAH will continue to monitor reports of low-energy subtrochanteric/ femoral shaft fractures in patients receiving alendronate therapy as part of routine pharmacovigilance activities.

2.5.7 Literature References

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[Exhibit 64 to Confoy Declaration]

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March 18, 2009

Food and Drug Administration
Center for Drug Evaluation & Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Sir or Madam:

Enclosed please find, in duplicate, "courtesy copies" of a Periodic Safety Update Report prepared for Fosamax® (alendronate sodium tablet and oral buffered solution, MSD). This report includes information received from 16-July-2008 through 15-January-2009.

Please be advised that this report is being provided to you for information until which time 21 CFR 314.80 is changed and a Periodic Safety Update Report replaces the required annual periodic adverse drug

experience report submissions to NDA 20-560 and 21-575.

Thank you for your attention to this matter.

Sincerely,

/s/ Linda S. Hostelley
Linda S. Hostelley
Vice President
Worldwide Product Safety & Quality Assurance

Enclosures

cc: S. Blumenthal
WORF
File

[Exhibit 65 to Confoy Declaration]

[redacted] ***Regulatory Liaison Telephone Conversation Record***

To	***Application or Project***	***Drug/Biologic/Compound***
[Direct Supervisor}	[Insert Application Type and # or project if appropriate.]	[Insert Trade, Generic or MK#]
David Altarac	NDA 20-560 NDA 21-762 NDA 21-575	Fosamax Tablets, Fosamax Plus, Fosamax Oral solution

Agency [Name of Agency Contacting]	***Agency Contact(s) / Title / Affiliation with the Agency*** [List each contact/ attendee. Use a hard carriage return (¶) to move to the next line.]
FDA	Dr. Scott Monroe, Divisional Director Reproductive and Urologic Products

Date(s) of Conversation(s)	***Merck Contact***
[dd-mmm-yyyy, e.g. 06-May-2006]	[List Merck Primary contact/ title. Insert add'l attendees at bottom of page]

9 April 2009 Charlotte B. Merritt

Subject:

Follow up on Labeling Supplements

Executive Summary [Note: Limit this field to 500 characters. Action should be captured in the Executive Summary.]

On April 7, I placed a call to Dr. Scott Monroe, Division Director for Reproductive and Urologic Products, to discuss with him the status of two outstanding submissions for the alendronate products. He returned my call on April 9. We first discussed Supplement 051 for FOSAMAX Tablets, which provided an update to the ONJ labeling. Dr. Kehoe (Medical Officer, Team Leader), who participated in the call with Dr. Monroe, indicated that FDA would be in the position to provide us a revised draft of the labeling in a few weeks following feedback from an internal consultation with dental experts. The subsequent discussion of Supplement 054 for FOSAMAX Tablets (which added language to the label related to subtrochanteric fractures) resulted in a suggestion by Dr. Monroe that, as an interim measure, we could amend the post-marketing section of the label only to include these data. The conversation ended cordially with my promise to get back to him shortly with our plans.

Detailed Summary [Note: This field has an unlimited number of characters.]

On April 7, I placed a call to Dr. Scott Monroe, Division Director for Reproductive and Urologic Products, to discuss with him the status of two

outstanding submissions for the alendronate products. He returned my call on April 9 and with him was Dr. Theresa Kehoe (Medical Officer, Team Leader). I thanked Dr. Monroe for returning my call and shared with him that Merck was anxious to understand FDA's timelines for completing their review of two labeling supplements and that this information had not been forthcoming from the Project Manager.

We discussed Supplement 051 for FOSAMAX Tablets, which provided an update to the ONJ labeling. The PDUFA data for this supplement was November 9, 2007. There have been several interactions with FDA and Merck on this supplement, but we had anticipated feedback on our latest response prior to the current time and would like to bring the interactions to completion so that we can print an updated label with the most current information. Dr Kehoe indicated that part of the delay was related to our request to add osteomyelitis (term added to draft labeling in April 2008 and all reports submitted in June 2008). In addition, she indicated that they have recently engaged some Dental colleagues and are expecting a recommendation from them in the next week or so. They will provide a revised draft of the labeling to us after this time, which can be the basis for a teleconference. Their goal is to craft separate class labels for oral and IV bisphosphonates.

We then discussed Supplement 054 for FOSAMAX Tablets, which added language to the label related to subtrochanteric fractures. Dr. Monroe indicated the duration of review was related to our elevation of this issue to a precaution in the labeling. He indicated that they could agree quickly to language in the post-marketing section of the labeling. FDA would like to

approach the issue of a precaution from the prospective of all bisphosphonates and are working with the Office of Safety and Epidemiology to do so. The conflicting nature of the literature does not provide a clear path forward, and more time will be need for FDA to formulate a formal opinion on the issue of a precaution around these data.

Prior to concluding our discussion, Dr. Monroe suggested that as an interim measure we may want to include a request to add text relating to subtrochanteric fractures to the post-marketing section of the label as part of our response to FDA's recent request (received April 6) to include Barrett's esophagus as an example of an active upper GI condition in which caution should be used when administering alendronate. I thanked him for this option and indicated that I would take this suggestion back to the team and would get back to him shortly. I also suggested that, if FDA was able to get back to us in a few weeks on the ONJ supplement, perhaps we could finalize that labeling as well in time to allow for a single printing including all three issues. Finally, Dr. Monroe reminded me that we also need to respond to their request for PLR by June. I indicated that I was aware of that request.

The conversation ended cordially with my promise to get back to him shortly with our plans. Alternatively, we agreed that Jim Adams may contact the Project Manager to follow up.

[Complete this section if actionable items have been identified.]

[If applicable, provide name only. Separate additional name]

[Exhibit 73 to Confoy Declaration]

FDA **U.S. Food and Drug Administration**
Protecting and Promoting Your Health

Drugs

Podcast for Healthcare Professionals: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures

Podcast[1]

Welcome, my name is Catherine Chew, a pharmacist in the Division of Drug Information. Today I am updating you about an ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures.

Healthcare professionals may have questions about oral bisphosphonate medications and atypical subtrochanteric femur fractures – fractures in the bone just below the hip joint.

Recent news reports have raised the question about whether there is an increased risk of this type of fracture in patients with osteoporosis using these medications. At this point, the data that FDA has reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures.

Based on published case reports of atypical subtrochanteric femur fractures occurring in women with osteoporosis using bisphosphonates, FDA, in June 2008, requested information from all

bisphosphonate drug manufacturers regarding this potential safety signal. All available case reports and clinical trial data were requested. FDA's review of these data did not show an increase in this risk in women using these medications.

In addition, FDA reviewed a December 2008 article in the *Journal of Bone and Mineral Research* by Abrahamsen and co-authors that analyzed data from two large observational studies in patients with osteoporosis. The authors concluded that atypical subtrochanteric femur fractures had many similar features in common with classical osteoporotic hip fractures, including patient age, gender, and trauma mechanism. The data showed that patients taking bisphosphonates and those not taking bisphosphonates had similar numbers of atypical subtrochanteric femur fractures relative to classical osteoporotic hip fractures.

The agency will continue to review new information as it becomes available and is working closely with outside experts, including members of the recently convened American Society of Bone and Mineral Research Subtrochanteric Femoral Fracture Task Force, to gather additional information that may provide more insight into this issue.

Once additional information is available, FDA will update the public about this issue.

At this time, FDA recommends that healthcare professionals:

1. Be aware of the possible risk of atypical subtrochanteric femur fractures in patients taking oral bisphosphonates.

2. Continue to follow the recommendations in the drug label when prescribing oral bisphosphonates.

3. Discuss with patients the known benefits and potential risks with using oral bisphosphonates.

4. Report any adverse events with the use of oral bisphosphonates to FDA's MedWatch program at www.fda.gov/medwatch.

Thank you for listening. The FDA is committed to keeping healthcare professionals informed of the latest safety information. If you have questions about this safety communication, you can reach the Division of Drug Information at the following email address: druginfo@fda.hhs.gov.

Related Information

- Podcast for Healthcare Professionals: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures - mp3 (MP3 - 7.1MB)[2]
- FDA Drug Safety Communication: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures[3]

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No. 17-290

IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,

Petitioner,

v.

DORIS ALBRECHT, ET AL.,

Respondents.

On Writ of Certiorari
To The United States Court of Appeals
For The Third Circuit

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QUESTION PRESENTED

In *Wyeth v. Levine*, 555 U.S. 555 (2009), this Court held that the FDA's approval of a drug label does not, standing alone, insulate the manufacturer from failure-to-warn liability under state tort law. At the same time, the Court recognized that if "the FDA would not have approved" the label demanded by state law, then the manufacturer could invoke an "impossibility" preemption defense. *Id.* at 571.

In this case, it was "undisputed" that (i) "the FDA was aware of the possible link" between petitioner's drug and the risk at issue; (ii) petitioner "submitted a comprehensive safety update to the FDA reporting ... numerous studies" finding "such an association"; (iii) petitioner "proposed warning language" about this risk, but the FDA "rejected" it; (iv) the FDA stated that the "conflicting nature of the literature d[id] not provide a clear path forward" and that it needed "more time" to consider "the issue of a precaution"; and (v) only later, after a report from a task force, did the FDA become "confident" that an association "potentially" existed. Pet.App.59a–60a.

The Third Circuit nonetheless held that a jury could find that petitioner had not shown by "clear and convincing evidence" that the FDA would have rejected a warning label of the type that respondents claim state law required. *See* Pet.App.37a, 56a–57a.

The question presented is: Is a state-law failure-to-warn claim preempted when the FDA rejected the drug manufacturer's proposal to warn about the risk after being provided with the relevant scientific data; or must such a case go to a jury for conjecture as to *why* the FDA rejected the proposed warning?

PARTIES TO THE PROCEEDING AND RULE 29.6 STATEMENT

Petitioner is Merck Sharp & Dohme Corporation, a wholly owned subsidiary of the entity formerly known as Schering Plough Corporation, which has been renamed Merck & Co., Inc. No publicly held corporation owns 10% or more of the stock of Merck & Co., Inc.

Respondents, listed in Appendix B, are more than five hundred plaintiffs who brought state-law failure-to-warn claims against Merck, alleging that they were injured by Merck's drug Fosamax prior to September 14, 2010. The Third Circuit resolved their appeals in one consolidated opinion. Pet.App.1a n.*. Pursuant to this Court's Rule 12.4, Merck filed a consolidated petition to challenge the Third Circuit's decision.

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INTRODUCTION

Merck told the FDA what it knew about the link between its drug Fosamax and the risk of atypical femoral fractures; Merck filed a formal request seeking FDA approval to add a warning to Fosamax's label addressing this risk; and the FDA rejected that request. In *Wyeth v. Levine*, this Court recognized that a pharmaceutical manufacturer cannot be held liable under state law for failure to warn about a health risk if the FDA would not have permitted the manufacturer to add that warning to its federally regulated label. 555 U.S. 555, 572–73 (2009). But unlike in *Levine*, here there is no need to guess what would have happened in a counterfactual world. It is clear that the FDA *would not* have allowed Merck to warn about the risk at issue because the FDA *did not* allow Merck to warn about it.

The Third Circuit nonetheless concluded that the preemption defense must be put to a jury—to decide as a counterfactual matter, while applying a unique, heightened standard of proof, whether the FDA might have approved a warning had Merck phrased it differently. That is misguided. The FDA's final agency action controls the preemption inquiry here as a matter of law. There is no room under either the Supremacy Clause or the federal drug labeling laws to speculate about *why* the agency blocked compliance with the alleged state-law duty.

Focusing on the meaning and scope of the FDA's actual decision also simplifies a set of related procedural questions that bogged down the Court of Appeals. Construing an agency's action is a question of law for the court to decide, not a factual dispute for a jury. And it does not implicate evidentiary

burdens of proof, which so concerned the Third Circuit. When, as here, the FDA has spoken by refusing to allow a warning (and there is no evidence it lacked any material information), a court must dismiss any state failure-to-warn claims as legally preempted.

OPINIONS BELOW

The district court's opinion granting judgment to petitioner, Pet.App.113a–52a, appears at 2014 WL 1266994. The Third Circuit's decision vacating and remanding, Pet.App.1a–95a, was reported at 852 F.3d 268.

JURISDICTION

The Third Circuit entered judgment on March 22, 2017, and denied petitioner's timely petition for rehearing on April 24, 2017. *See* Pet.App.1a, 175a–76a. Justice Sotomayor extended the time to file a certiorari petition until August 22, 2017, *see* No. 16A1264, on which day Merck filed. This Court has jurisdiction under 28 U.S.C. § 1254(1).

PROVISIONS INVOLVED

Relevant statutory and regulatory provisions are reproduced in Appendix A.

STATEMENT

A. Statutory and Regulatory Framework.

1. Labeling is the "centerpiece" of the FDA's "risk management" strategy for prescription drugs, and the primary method by which it communicates its conclusions about when and how drugs can be safely used. FDA, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3922, 3934

(2006). Because of labeling's central role, the FDA has final say over a prescription drug's label throughout the drug's lifespan.

Before a new, brand-name drug can be approved, the manufacturer must submit "specimens of the labeling proposed to be used for such drug." 21 U.S.C. § 355(b)(1). (Generic drugs must use the label approved for the brand-name version. *Id.* § 355(j)(2)(A)(v).) The FDA uses those submissions when deciding whether the drug is "safe for use under the conditions prescribed, recommended, or suggested" in its "labeling." *Id.* § 355(d).

2. "Despite the rigorous steps in the process" of approving a drug, "the true picture of a product's safety actually evolves over the months and even years that make up a product's lifetime." FDA, *Step 5: FDA Post-Marketing Drug Safety Monitoring* (Jan. 4, 2018), https://perma.cc/QU75-KDAC. Both the manufacturer and the FDA have roles to play in ensuring that a drug's label evolves alongside its risk profile.

a. The manufacturer must ensure that the label adequately warns of the drug's risks in light of new evidence. *See Levine*, 555 U.S. at 570–71 ("[T]he manufacturer bears responsibility for the content of its label at all times."). So the manufacturer must seek to revise its label "as soon as" the evidence justifies a change. 21 C.F.R. § 201.57(c)(6)(i); *see also id.* § 201.57(c)(7). A manufacturer may discharge this duty in one of two ways. But, either way, the FDA reviews the proposed label under the same regulatory standard, and "retains authority to reject" the manufacturer's proposed "labeling changes." *Levine*, 555 U.S. at 571.

First, through the so-called "Changes Being Effected" (or "CBE") process, a manufacturer may revise the label and begin distributing the relabeled product immediately upon submitting an application requesting FDA approval. This process is available "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling" under the FDA's regulatory standards. 21 C.F.R. § 314.70(c)(6)(iii)(A). But if the FDA ultimately rejects the application, it may "order the manufacturer to cease distribution" of the drugs already "made with the manufacturing change." *Id.* § 314.70(c)(7).

Second, manufacturers may seek the agency's advance permission by submitting a Prior Approval Supplement, or "PAS." "Historically," the FDA has "accepted PAS applications instead of CBE supplements," "particularly where significant questions exist on whether to revise or how to modify existing drug labeling." U.S. Cert. Br. 5. Thus, "in practice, manufacturers typically consult with FDA prior to adding risk information to labeling," 71 Fed. Reg. at 3934, to avoid the waste and confusion that would otherwise result if the FDA later disapproved the changes. As with CBE applications, the FDA will reject a manufacturer's PAS if it concludes that the proposed changes do "not comply with the requirements for labels" in the applicable regulations. 21 C.F.R. § 314.125(b)(6), (b)(8).

b. Although drug manufacturers bear primary responsibility for their own labels, the FDA

also has its own statutory obligation to ensure that warning labels are complete, correct, and up-to-date.

Under statutory amendments that took effect in 2007—after the events at issue in *Levine*, but before those at issue here—if the FDA "becomes aware of new safety information that ... should be included in the labeling of the drug," then the agency "shall promptly notify" the manufacturer. 21 U.S.C. § 355(*o*)(4)(A). Then, the manufacturer must either "submit a supplement proposing changes to the approved labeling to reflect the new safety information" or explain why it "does not believe a labeling change is warranted." *Id.* § 355(*o*)(4)(B).

If the FDA "disagrees" with the manufacturer's response, it "shall initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes." *Id.* § 355(*o*)(4)(C). Of course, the FDA has the final say in those discussions; it "may issue an order directing [the manufacturer] to make such a labeling change as [it] deems appropriate to address the new safety information." *Id.* § 355(*o*)(4)(E); *cf.* § 355(*o*)(4)(F) (appeals process).

Consistent with its statutory obligation, the FDA works cooperatively with manufacturers when they seek approval for new drugs or revised labeling. Throughout the approval process for new drugs, the FDA "communicate[s] with applicants about scientific, medical, and procedural issues that arise." 21 C.F.R. § 314.102(a). If it spots "easily correctable deficiencies," it will "make every reasonable effort to communicate" those deficiencies "promptly," so as "to permit the applicant to correct" them "relatively

early in the review process." *Id.* § 314.102(b). Similarly, "if the only deficiencies in [an application] concern editorial or similar minor deficiencies in the draft labeling," the "FDA will approve" the application "conditioned upon the applicant incorporating the specified labeling changes exactly as directed." *Id.* § 314.105(b).

The FDA applies the same principles to supplemental applications submitted through the CBE and PAS processes. *See* 21 C.F.R. § 314.71(b), (c); U.S. Cert. Br. 5. If the agency agrees that a label revision is warranted, it will work with the manufacturer to develop appropriate language. *See* U.S. Cert. Br. 5–6, 21–22. But if the FDA concludes that the proposed warning is scientifically unjustified, it will deny the applicant's request in a "complete response letter." 21 C.F.R. § 314.110(a). That letter generally "describe[s] all of the specific deficiencies that the agency has identified" in the application and, "[w]hen possible," "will recommend actions that the applicant might take to place the application ... in condition for approval." *Id.* § 314.110(a)(1), (a)(4); *see also* U.S. Cert. Br. 5–6.

B. Fosamax and Its Label.

1. In healthy bone tissue, new bone cells slowly replace old ones. *See* Liza J. Raggatt & Nicola C. Partridge, *Cellular and Molecular Mechanisms of Bone Remodeling*, 285 J. Biological Chem. 25103, 25103–07 (2010). In some post-menopausal women, that process falters: more bone is removed than is replaced, leaving less dense bones that are more likely to break. *See* Pet.App.5a. This altered process can lead to osteoporosis.

In 1995, the FDA approved alendronate—better known as Fosamax, a Merck product—to treat osteoporosis in postmenopausal women. Pet.App.12a. Fosamax is a type of bisphosphonate, a class of drugs that slow down the removal of old bone cells. In this way, it maintains the balance between removal and replacement and helps patients retain bone mass. "Solid evidence" demonstrates that Fosamax "decreas[es] the risk of vertebral fracture (by 40% to 70%), hip fractures (by 20% to 50%), and nonvertebral fractures (by 15% to 39%)." Robert A. Adler, et al., *Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research*, 31 J. Bone & Mineral Research 16, 16–17 (2015).

But the mechanism that makes Fosamax a success—the way it slows down bone removal—could theoretically increase the risk of other fractures. Some have hypothesized that bisphosphonates "may inhibit microdamage repair by preventing ... bone resorption at the sites of microdamage," creating small cracks that might then progress into more serious fractures. Pet.App.12a.

2. Merck has long worked with the FDA to ensure that Fosamax's label adequately warns of its risks. In 1992, Merck brought the theoretical considerations mentioned above to the FDA's attention during the approval process. The agency approved Fosamax's label without requiring any mention of this hypothetical risk. Pet.App.12a–13a. Merck then continually provided the FDA with updates about the data, adverse events, and literature available after Fosamax reached the

market. Pet.App.13a ("Merck kept the FDA informed of ... studies suggesting a possible association between bisphosphonates and fractures.").

Over time, evidence began to emerge that a very small percentage of long-term bisphosphonate users—and some non-users—suffered from what later came to be known as atypical femoral fractures. To understand these fractures, it helps to understand the nomenclature sometimes used (although inconsistently) to describe different types of bone injuries. Traumatic fractures result from the application of extraordinary force to a bone, and low-energy fractures occur absent such force. Certain low-energy fractures are sometimes called "stress fractures" or "insufficiency" fractures. *See* Richard H. Daffner & Helene Pavlov, *Stress Fractures: Current Concepts*, 159 Am. J. Radiology 245, 245–46 (1992); U.S. Cert. Br. at 8 n.7.

Atypical femoral fractures are low-energy fractures that occur in the long shaft of the femur (the "diaphyseal" region) or in the portion below the part of the femur that forms the hip (the "subtrochanteric" region). In March 2008, Merck provided the FDA with a periodic safety update that included "over 30 pages of information regarding" these fractures. Pet.App.14a. Merck also noted that "[r]ecent publications" "implicated a link between prolonged bisphosphonate therapy and atypical low-energy non-vertebral fractures." Pet.App.14a. Shortly afterwards, Merck sent the FDA a copy of a letter in the New England Journal of Medicine that provided additional "evidence of a potential link between [prolonged] alendronate use and low-energy

fractures of the femur." Brett A. Lenart, et al., *Atypical Fractures of the Femoral Diaphysis in Postmenopausal Women Taking Alendronate*, 358 New England J. Med. 1304, 1305 (Mar. 20, 2008); *see* Pet.App.14a.

In June 2008, the FDA told Merck that it was "aware of reports regarding" atypical femoral fractures "in patients using bisphosphonates," and cited several of the key articles. J.A.280–81. It asked Merck and other bisphosphonate manufacturers for more information about this "developing safety signal." J.A.280. Merck "promptly complied." Pet.App.14a.

3. While the FDA was "analyzing Merck's data," Merck sought approval to revise Fosamax's label to include the risk of atypical femoral fractures. Pet.App.14a. Merck submitted PASs requesting revisions to Fosamax's labels to address "low-energy fractures that have been reported, of which some ha[d] been stress/insufficiency, at the subtrochanteric region of the femoral shaft." J.A.670. Merck acknowledged that it was not possible "to establish whether treatment with alendronate increases the risk of low-energy subtrochanteric and/or proximal femoral shaft fractures." *Id.* But Merck still "believe[d] that it [wa]s important to include an appropriate statement about them in the product label," given their "clinical importance" and "their temporal association with bisphosphonate use." *Id.*

In particular, Merck sought to revise two sections of Fosamax's labels: the Adverse Reactions section and the Warnings and Precautions section. To include an adverse event in the Adverse Reactions

section, there must be "some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event." 21 C.F.R. § 201.57(c)(7). Merck proposed adding "low-energy femoral shaft fracture" to the Fosamax label's "Adverse Reactions" section. Pet.App.16a.

Merck also sought to revise the Warnings and Precautions part of the label. For that, the causal link between the drug and an adverse reaction must be more certain—there must be "reasonable evidence of a causal association with a drug." 21 C.F.R. § 201.57(c)(6)(i). In addition, the Warnings and Precautions section is reserved for adverse reactions that are more clinically significant than those listed only in the Adverse Reactions section of the label. *See* FDA, *Supplemental Applications Proposing Label Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 49603, 49605–06 (2008) (FDA's standard is designed to "prevent overwarning" so that less important information does not "overshadow more important warnings"); U.S. Cert. Br. 3.

Merck sought to revise this section of Fosamax's labels to state:

> Low-Energy Femoral Shaft Fracture
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often

> associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.

Pet.App.15a–16. In the accompanying materials, Merck described the reports that it had received of "low-energy subtrochanteric/femoral shaft fractures," J.A.748, identified numerous studies addressing the subject, J.A.757–61, and explained its chosen terminology, J.A.746.

4. The FDA responded in a complete response letter issued on May 22, 2009. J.A.510–13. It "agree[d] that atypical and subtrochanteric fractures should be added to the ADVERSE REACTIONS" portion of Fosamax's labels. J.A.511. It "recommend[ed]" a minor change to Merck's drafting, suggesting that Merck add "low energy femoral shaft *and subtrochanteric* fractures" (rather than just

"low-energy femoral shaft fractures"). J.A.512 (emphasis added).

As for the Warnings and Precautions section, however, the FDA rejected Merck's request, and cited the following "reasons":

> [Y]our justification for the proposed PRECAUTIONS section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting.

J.A.511–12.

The FDA's split decision—rejecting a warning about atypical femoral fractures while approving an addition to Fosamax's Adverse Reactions label about the very same risk—tracked Merck's back-and-forth with agency officials. In April 2009, the FDA official who later authored the complete response letter told Merck that the agency could "agree to add language in the Adverse Reactions section," but that Merck's "elevation of the issue to a precaution" was "prolonging review," as "the conflicting nature of the literature d[id] not provide a clear path forward." Pet.App.17a. Later, another FDA official similarly told Merck by email that its "currently pending" PASs "could be approved at this time only for inclusion of the atypical fracture language proposed in the postmarketing adverse events section," but "[i]f Merck agree[d] to hold off on the W&P language

at this time," the FDA could "close out th[o]se supplements" and then "work with ... Merck to decide on language for a W&P atypical fracture language, if it is warranted." J.A.508.

In June 2009, Merck issued new labels implementing the FDA's revisions to its Adverse Reactions proposal. J.A.274, 279.

5. The FDA continued to review the possible relationship between bisphosphonates and atypical femoral fractures. In a March 2010 Drug Safety Communication, the FDA explained that "the data ... reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures." J.A.519; *see also* J.A.520 (discussing how FDA's analysis of manufacturers' data "did not show an increase in [the risk of atypical femoral fractures] in women using these medications"); J.A.520 (discussing a December 2008 study that showed "similar numbers of atypical subtrochanteric femur fractures" regardless of use of bisphosphonates). The FDA therefore advised doctors to "[b]e aware" of this issue, but to "[c]ontinue to follow the recommendations in the [unrevised] drug label." J.A.521. The FDA also explained that it was "working closely with outside experts," including those from a task force assembled by the American Society of Bone and Mineral Research, "to gather additional information that may provide more insight into this issue." J.A.519–20.

The task force published its first report in September 2010. It noted that "[t]he radiologic presentation of atypical femoral fractures bears striking similarities to that of stress fractures."

Elizabeth Shane, et al., *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research*, 25 J. of Bone & Mineral Research 2267, 2270 (2010) ("*First Report*"); *see also* Elizabeth Shane, et al., *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society for Bone and Mineral Research*, 29 J. of Bone & Mineral Research 1, 10–12 (2014) (later concluding that the "evidence suggests that [atypical femoral fractures] are stress fractures"). The task force crafted a "provisional case definition" of the "features for complete and incomplete atypical [femoral] fractures," and it reassessed prior studies in light of that definition. *First Report*, 25 J. of Bone & Mineral Research at 2268–69. The task force concluded that "a causal association between [bisphosphonates] and atypical fractures ha[d] not been established." *Id.* at 2267. Nonetheless, because "recent observations suggest[ed] that the risk rises with increasing duration of exposure," the task force recommended that "[p]hysicians and patients should be made aware of the possibility of atypical femoral fractures." *Id.*

6. The FDA responded immediately. It explained that the task force's case definition would "help greatly in identifying cases and reporting on them, and should facilitate future studies" assessing any causal link between "these unusual fractures" and bisphosphonate use. J.A.523. The FDA also recognized that the task force "recommended changes to product labels," which the agency was

"considering" as part of its "thorough[] review[]" of "all long term data available." J.A.524–25.

A month later, the FDA announced that, "[a]lthough it is not clear if bisphosphonates ... cause" atypical femoral fractures, information about them would be "added to the ***Warnings and Precautions*** section of the labels of all bisphosphonate[s]." J.A.246, 247. The Deputy Director of the Office of New Drugs, an FDA official, explained that the task force's report "helped to clarify the features of atypical femur fractures" and "provide[d] more information that more closely associate[d] these atypical fractures with long-term bisphosphonate use." J.A.488–89. That is, the task force's report "really helped" the agency conclude that atypical femoral fractures are "something that is potentially more closely related to these drugs, particularly long-term use than we previously had evidence for." J.A.494.

Citing both the task force report and its duties under section 355(*o*)(4), the FDA wrote to Merck to propose changes to the Warnings and Precautions section of Fosamax's labels. J.A.526–34. Merck responded with suggested revisions, including "to make clear that doctors should attempt to rule out stress fractures," so that complete fractures could be avoided. Pet.App.22a. Although the FDA accepted some of Merck's proposed changes, it rejected Merck's stress-fracture-related ones, noting the agency's belief that, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use." J.A.566. "In addition, the risk factors listed in

the proposed changes have not been sufficiently validated to include in the labeling at this time." *Id.* Merck revised Fosamax's labels according to the FDA's instruction. Pet.App.23a.

C. This Litigation.

1. After Merck changed its label, many Fosamax users who had allegedly suffered atypical femoral fractures sued. They generally alleged that Merck failed to warn about this risk. Pet.App.23a–24a. Over a thousand cases were sent to a multi-district litigation proceeding in the District of New Jersey. Pet.App.23a. The District Court litigated several bellwether cases—with *Glynn v. Merck Sharp & Dohme Corp.*, No. 11:cv-05304 (D.N.J.), being the first to proceed to trial—to see whether those cases could resolve any issues pertinent to the other thousand-plus cases. Pet.App.115a.

Federal preemption was one such global issue. Drug manufacturers may not be held liable under state tort law if the FDA prevented or would have "prevented [them] from adding a stronger warning." *Levine*, 555 U.S. at 573; *see also id.* at 571 (rejecting Wyeth's preemption defense because it lacked "clear evidence that the FDA" would have rejected a stronger warning). From the beginning, Merck told plaintiffs and the District Court that preemption would be critical to its defense, and the various parties conducted discovery into Merck's dealings with the FDA accordingly. *See* Pet.App.116a.

After discovery, Merck moved for summary judgment in *Glynn*, arguing that the claims were preempted by the FDA's rejection of Merck's proposed warning. Pet.App.116a. But the District

Court wanted to resolve the issue based on a full record, so it allowed the case to proceed to trial. Pet.App.116a. After trial, the District Court granted Merck's motion. Pet.App.168a. It recognized that impossibility preemption "'is a demanding defense.'" Pet.App.168a (quoting *Levine*, 555 U.S. at 573). It nevertheless concluded that there was "clear evidence that the FDA would not have approved a change to the Precautions section of the Fosamax label" before the September 2010 task force report. *Id.*

"Throughout the entire pre-trial, trial, and post-trial proceedings in *Glynn*, the [District Court] made it clear that ... it wanted the parties to introduce any and all relevant evidence [regarding preemption] because of the effects it could have on the MDL as a whole." Pet.App.124a; *see also* Pet.App.124a–129a (detailing the court's efforts). The District Court followed through by ordering plaintiffs whose alleged injuries occurred before the task force's report to show cause why their claims were not preempted like Glynn's. Pet.App.129a–30a. After thus providing these plaintiffs with yet another "opportunity to identify genuine issues of material fact" on that issue, Pet.App.136a, the District Court held their claims preempted. Pet.App.152a. It also found that some of the plaintiffs' other claims were failure-to-warn claims in disguise, and thus preempted for the same reason. Pet.App.139a–46a.

2. The Third Circuit vacated and remanded. It first held that *Levine*'s reference to "clear evidence" created a heightened standard of proof: to prevail on a preemption defense, "[t]he manufacturer must prove that the FDA would have rejected a warning

not simply by a preponderance of the evidence, as in most civil cases, but by 'clear evidence,'" which the court equated with the more familiar "clear-and-convincing-evidence" standard. Pet.App.35a–36a, 37a. According to the Third Circuit, the defendant must prove it is "*highly probable*" that the FDA would have rejected the change. Pet.App.37a (emphasis added).

The court also held that whether the FDA would have rejected the proposed change is a jury question, even when the historical facts are undisputed, because the inquiry is "counterfactual." Pet.App.54a. A manufacturer thus cannot establish the preemption defense as a matter of law, pre-trial, absent a "'smoking gun' rejection letter from the FDA" that would leave a jury no choice but to find the state-law claim preempted. Pet.App.55a.

Applying that framework, the Third Circuit found no smoking gun here. It acknowledged the considerable strength of Merck's position. Prior to the task force report, the FDA had repeatedly expressed doubt about the evidence tying bisphosphonate use to atypical femur fractures, including in rejecting Merck's proposed warning. Pet.App.59a–61a. To prevail, respondents would have to persuade juries to overlook this evidence and to conclude that the FDA spurned Merck's proposal not because it doubted the underlying data or need for a warning, but for some other, curable deficiency that it refused to help Merck resolve. In other words, respondents would have to prove that the FDA chose to leave patients uninformed rather than working with Merck on acceptable language. Pet.App.61a–62a.

Although the court did not "discount the force of [Merck's] evidence," it concluded that a jury could still find it less than "highly probable" that the FDA would have rejected a label change had Merck simply phrased it differently. Pet.App.62a–63a. In its view, a jury could interpret the statements and actions of a federal regulatory authority and conclude that the FDA's rejection was all about Merck's terminology (for example, its use of the term "stress fractures"), and that the agency had flatly rejected the proposal for that reason rather than offer alternative language (as the law commands it to do). Pet.App.67a. Thus, "a reasonable jury applying a heightened standard of proof *could* conclude" that the FDA would have allowed a label change. Pet.App.67a. The Third Circuit therefore remanded the claims for trial (including the disguised failure-to-warn claims, which had been dismissed by the District Court on derivative grounds). Pet.App.74a.

3. Merck petitioned for certiorari. The Court called for the views of the Solicitor General. *See* 138 S. Ct. 533 (2017) (mem.). In response, the United States made two critical points.

First, the United States explained that the FDA does not reject scientifically justified warnings because of disagreement with a manufacturer's phrasing. *See* U.S. Cert. Br. 5–6, 21–22. To do so would be inconsistent with the FDA's own regulations. *See* U.S. Cert. Br. 5–6, 21; *supra* pp. 5–6. It would also violate the agency's statutory obligation to work with manufacturers on revised labeling. *See supra* pp. 4–5; U.S. Cert. Br. 22.

Second, the United States explained that the FDA's actions surrounding Fosamax reflected that

general approach. That is, the FDA rejected Merck's particular proposal because of "the agency's determination that the data was then insufficient to justify such a warning." U.S. Cert. Br. 19. That reasoning was set forth in the FDA's complete response letter, which stated that Merck's "justification for the proposed ... language was inadequate." U.S. Cert. Br. 20 (emphasis omitted). It was not until "October 2010—after [the] task force['s] report"—that the FDA "came to 'believe that the information' about atypical femoral fractures should be added to the Warnings and Precautions section and therefore invoked Section 355(*o*)(4) to revise the labeling for Fosamax and other bisphosphonates." U.S. Cert. Br. 22 (quoting J.A.527).

SUMMARY OF ARGUMENT

If a manufacturer proposes to warn about a risk, discloses what it knows about that risk, and gets rebuffed by the FDA, failure-to-warn claims against it are preempted as a matter of law.

I. States may not require what federal law forbids. Accordingly, state tort law may not penalize drug manufacturers for failing to revise their labels in ways that federal law would not have allowed. It follows that, where the FDA rejects a manufacturer's proposal to warn about a disclosed risk, failure-to-warn claims premised on that risk are preempted.

A. In *Levine*, the Court acknowledged that, if the FDA would have prevented a manufacturer from revising its label as state law supposedly demanded, state-law claims premised on its failure to revise its label would be preempted. *See* 555 U.S. at 571–72.

In that case, however, the manufacturer could not make such a showing. It never tried to warn about the risk in question and was never "prohibited from doing so by the FDA." *Id.* at 572. Indeed, it did not even "suppl[y] the FDA with an evaluation or analysis" about that risk, and could not prove that the FDA "gave more than passing attention" to it. *Id.* at 572–73. Absent "clear evidence" that the FDA would have rejected the warning plaintiffs claimed state law required, state-law failure-to-warn claims against it could proceed. *Id.* at 571.

In two later cases, however—*PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011), and *Mutual Pharmaceutical Co. v. Bartlett*, 570 U.S. 472 (2013)—this Court explained that plaintiffs cannot avoid preemption through mere speculation about how a manufacturer could comply simultaneously with both state and federal law. In *Mensing*, the plaintiffs sued defendants that, as generic manufacturers, could not change their own labels. The Court held that even if the manufacturers might have been able to convince the FDA to change the brand-name drug's label, such "conjecture[]" does not "suffice to prevent federal and state law from conflicting for Supremacy Clause purposes." 564 U.S. at 621. And in *Bartlett*, this Court held that the mere possibility that the manufacturer could simultaneously "comply" with state and federal law by withdrawing from the market could not defeat preemption either. *See* 570 U.S. at 489–90.

B. These cases establish that failure-to-warn claims are preempted if a manufacturer proposes to warn about a risk, discloses the relevant information, and is turned back. In such situations,

it is impossible to comply with both state and federal law: the FDA "*would not* have approved a change" to the label, *Levine*, 555 U.S. at 571 (emphasis added), where the FDA *did not* approve a change to the label.

The applicable statutory and regulatory regime further demonstrates that the FDA's rejection of a proposal ends the matter. The FDA now has a statutory obligation to respond to new safety information by working with a manufacturer toward—or ordering a manufacturer to implement—appropriate revisions. *See* 21 U.S.C. § 355(*o*)(4). And the FDA's own regulations require it to correct poorly phrased or otherwise procedurally flawed but scientifically justified warnings, not to leave patients in the dark. The FDA's rejection of a proposed warning thus reflects its conclusion that no warning should be given. State tort law cannot second-guess that conclusion.

C. Respondents' failure-to-warn claims are preempted under these straightforward principles. Merck "kept the FDA informed" about the "possible connections" between bisphosphonate use and atypical femoral fractures. Pet.App.13a. Merck then sought to "add language to the ... Warnings & Precautions ... section[] of [Fosamax's] label" to address "atypical femoral fractures." Pet.App.15a. But the FDA rejected that request, reasoning that Merck's "justification" was "inadequate." J.A.511. Respondents' failure-to-warn claims are therefore preempted, because it was impossible for Merck to revise its label as they demand.

II. The Third Circuit reached a contrary conclusion because, in its view, a rational jury "could find it less than highly probable" that the FDA would

have rejected a *differently phrased* warning about atypical femoral fractures. Pet.App.56a–57a. Its conclusion reflects a basic misunderstanding of the regulatory regime and this Court's precedents.

A. The Third Circuit treated the relevant question as counterfactual. Rather than focusing on the FDA's actual decision, it asked what the FDA would have done had Merck proposed a different warning. That approach was mistaken in circumstances like these. Where the FDA has flatly rejected a manufacturer's request to add a warning, that rejection says everything one needs to know about whether the manufacturer could have complied with state and federal law.

In *Levine*, the Court *had* to inquire into what would have happened had Wyeth proposed a warning, because Wyeth had not in fact done so. There was no agency action directly addressing the health risk in question. That says nothing about the proper approach in a case like this one, where the manufacturer tried to provide a warning and the FDA said no.

Nor would speculation about what might have happened had Merck rephrased its proposal lead to a different result. The FDA does not disregard its statutory and regulatory duties and leave patients in the lurch when manufacturers propose scientifically justified warnings but need editorial assistance in articulating them. The contrary notion—advanced by respondents and credited by the Third Circuit—runs headlong into the presumption of regularity, not to mention the well-established principle that speculation may not defeat preemption.

B. Once one recognizes that what matters is what the FDA did with Merck's actual proposal—not ill-advised conjecture about what it might have done with a different one—the Third Circuit's related errors become apparent.

For example, the Third Circuit concluded that its hypothetical question presents a question of fact. But the real question here—the meaning and effect of the FDA's actual action—presents an obvious question of law, as all parties agree. Similarly, the Third Circuit concluded that its hypothetical question belonged to the jury rather than the judge. But questions of law must be resolved by a judge, not by a thousand different juries deciding individual cases. Finally, the Third Circuit concluded that manufacturers must prove what the FDA would have done by clear and convincing evidence. But questions of law are resolved without reference to such burdens of proof.

Even if the Third Circuit's general approach to the preemption question were correct, its answers to these related questions would be wrong. Whether or not the FDA would have approved a differently worded proposal is a fundamentally legal question about how the FDA would have applied its regulations in the context of an undisputed record of scientific data, not (as the Third Circuit seemed to think) an unbounded psychoanalysis of agency officials and their motives. And even if the Third Circuit's hypothetical question presents a question of fact, manufacturers need not make their case by clear and convincing evidence. Absent a statutory command, courts generally reserve such a heightened standard for truly compelling interests—

stripping parental rights, involuntarily committing the mentally ill, and the like. The tort suits here do not present such interests. And nothing in *Levine*—which used the phrase "clear evidence" only once, in passing—holds otherwise.

III. Finally, even if the law were exactly as the Third Circuit believed, Merck would still prevail here. The FDA's brief to this Court removes any possible doubt that, before October 2010, Merck could not have warned of the risk of atypical femoral fractures. The FDA has now declared that it rejected Merck's warning because of "the agency's determination that the data was then insufficient to justify such a warning," not because of concerns about Merck's "proposed text." U.S. Cert. Br. 19. The agency has also declared that it did not believe the data justified a warning about atypical femoral fractures until "October 2010," after the task force report. U.S. Cert. Br. 22.

No rational juror could get past this evidence, even applying a heightened burden of proof. To conclude otherwise, this Court would have to disregard the deference owed to an agency's explanation of its decision. And it would also have to ignore the record in this case, which supports the agency's current explanation of its decision at every turn. Because the FDA itself has now provided the very "smoking gun" the Third Circuit demanded, respondents' claims must fail.

Nonetheless, because of the practical importance of these recurring legal issues in ongoing pharmaceutical litigation across the nation, this Court should address the broader issues raised in this case.

ARGUMENT

I. When the FDA Rejects a Manufacturer's Proposal To Warn About a Disclosed Risk, the Manufacturer Cannot Be Penalized for Failing To Warn of That Risk.

The Supremacy Clause says: "This Constitution, and the Laws of the United States which shall be made in Pursuance thereof ... shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const. art. VI, cl. 2. Simply put, "where state and federal law directly conflict, state law must give way." *Wos v. E.M.A. ex rel. Johnson*, 568 U.S. 627, 636 (2013). And federal law "directly conflicts" with state law when it is "impossible for a private party to comply with both state and federal requirements." *English v. Gen. Elec. Co.*, 496 U.S. 72, 79 (1990); *see also Levine*, 555 U.S. at 589–90 (Thomas, J., concurring in the judgment). Consequently, courts may not enforce state laws that require what federal law forbids, or forbid what federal law requires.

As explained below, a state may not impose tort liability on a drug manufacturer for failing to warn of a risk that the FDA would not have permitted the manufacturer to warn about. Under those circumstances, the state would be penalizing a party for not taking action that federal law forbade. And when, as here, the FDA *rejected* a request by the manufacturer to warn of the risk, there is no doubt that state failure-to-warn claims are preempted. Indeed, it is hard to imagine a more obvious case of impossibility preemption.

A. Failure-To-Warn Claims Are Preempted If Federal Law Would Have Forbidden the Manufacturer To Revise Its Label.

This Court has considered preemption in the specific context of pharmaceutical labeling in a trio of recent decisions: *Levine*, *Mensing*, and *Bartlett*. Read together, these cases establish that a state may impose failure-to-warn liability only if the FDA would not have stood in the way of the manufacturer's warning about the risk at issue.

1. In *Levine*, the plaintiff successfully argued to the Vermont state courts that the label for Wyeth's drug Phenergan should have more strongly advised doctors to administer the drug indirectly through IV-solution (the "IV-drip" method) rather than directly into the vein (the "IV-push" method). 555 U.S. at 560–63. Wyeth argued in this Court that the "FDA's approvals" of Phenergan's label categorically created "a complete defense" to the tort claims. *Id.* at 558–59. In Wyeth's view, "it would have been impossible for it to comply with the state-law duty to modify Phenergan's labeling without violating federal law," *id.* at 563, because it had no power to change its label without FDA's permission.

This Court rejected Wyeth's claim of impossibility. It agreed in principle that, if federal law had prevented Wyeth from updating its label, then the failure-to-warn claim would have been preempted. *Id.* at 571–72. But federal law is not that inflexible. Manufacturers do have the power to change their labels, so long as the FDA approves. *Id.*

Because Wyeth never sought to revise its label, the dispositive question for preemption purposes was

whether the FDA would have approved or rejected a stronger IV-push warning had Wyeth sought one. And, on that question, the Court found no "clear evidence that the FDA would not have approved a change to Phenergan's label." *Id.* at 571. Indeed, Wyeth "offered no such evidence." *Id.* at 572. Wyeth did "not argue that it supplied the FDA with an evaluation or analysis" about "the specific dangers posed by the IV-push method." *Id.* at 572–73. The record showed that neither the FDA nor Wyeth "gave more than passing attention to the issue." *Id.* at 572. Nor did Wyeth try to warn about the risks of IV-push, only to be "prohibited from doing so by the FDA." *Id.* To be sure, the FDA had approved Phenergan's label when it first approved the drug for sale. The "mere fact" of approval, however, did not make compliance impossible. Wyeth could have pursued a revision through the CBE process, and failed to show that the FDA would have objected. *Id.* at 573; *see also id.* at 593 (Thomas, J., concurring in the judgment).

Levine thus applied basic preemption principles to drug labeling. While the FDA's *approval* of a label does not itself insulate the manufacturer from tort liability, a manufacturer cannot be held liable for failing to give a warning that the FDA would have disapproved had it been asked.

2. A few years later, this Court in *Mensing* clarified that mere *speculation* about ways in which the manufacturer might have been able to reconcile its federal and state-law duties cannot save a plaintiff's claim from preemption.

In *Mensing*, the plaintiffs alleged that a generic-drug manufacturer failed to warn about a severe

neurological disorder. 564 U.S. at 609. But unlike their brand-name counterparts, manufacturers of generic drugs cannot use the CBE or PAS process. Instead, they "have an ongoing federal duty of 'sameness'"—their labeling "must be the same as the listed drug product's labeling." *Id.* at 613 (quoting 57 Fed. Reg. 17950, 17961 (1992)). As a result, this Court held that it was "impossib[le]" for generic manufacturers to comply with both state and federal law: state law supposedly required a "safer label," but federal law "demanded" a label that matched the brand-name drug's. *Id.* at 618–19.

The plaintiffs argued that the manufacturers could have taken other steps to try to get the brand-name drug's label changed. For instance, they argued (and the Court assumed) that the generic manufacturers had (and breached) a duty to alert the FDA about newly recognized risks. *See id.* at 619. Had that alert been given, it was "certainly possible" that the FDA might have ordered changes to the brand-name label, so that the generic manufacturers "might have eventually been able to strengthen their warning label" too. *Id.* at 620. But because preemption turns on "whether the private party could independently do under federal law what state law requires of it," these "conjectures" did not "suffice to prevent federal and state law from conflicting." *Id.* at 620–21; *see also id.* at 623 (plurality op.) (refusing to consider such "inherent" "contingencies" because "pre-emption analysis should not involve speculation about ways in which federal agency and third-party actions could potentially reconcile federal duties with conflicting state duties").

3. The final case, *Bartlett*, reiterated the two key takeaways from *Levine* and *Mensing*: state law cannot require label revisions that federal law prohibits, and speculative means of dual compliance do not defeat impossibility preemption.

Bartlett involved New Hampshire's design-defect regime, which put a choice to drug manufacturers: either redesign the drugs to make them safer or add a stronger warning. 570 U.S. at 482–84. This Court held that federal law precluded a generic manufacturer from taking either option; it could not alter the drug's composition without thereby creating "a new drug that would require its own NDA," *id.* at 484, and it could not revise its label without running afoul of *Mensing* and the duty of sameness, *see id.* at 486. Because "federal law prohibited ... the remedial action required to avoid liability under New Hampshire law," the claims were preempted. *Id.*

Bartlett also reiterated that plaintiffs cannot avoid preemption by conjuring up speculative scenarios or faux alternatives. The plaintiff in *Bartlett* argued that the manufacturer *could* comply with federal and state law by taking its products off the shelves in New Hampshire. This Court refused to allow that supposed option to defeat preemption. "Our pre-emption cases presume that an actor seeking to satisfy both his federal- and state-law obligations is not required to cease acting altogether in order to avoid liability." *Id.* at 488. "Just as the prospect that a regulated actor could avoid liability ... by simply leaving the market did not undermine the impossibility analysis in [*Mensing*], so it [was] irrelevant" to the Court's analysis in *Bartlett*. *Id.* at 489–90.

B. Where the FDA Rejects a Request To Add a Warning, Failure-To-Warn Claims Are Preempted.

Levine already established that, even if a manufacturer does *not* seek to revise its label, failure-to-warn claims against it are still preempted if the manufacturer can prove that the FDA would have rejected its attempt. *See* 555 U.S. at 571–72. But *Levine*, *Mensing*, and *Bartlett* also establish a corollary applicable here: if a manufacturer does propose to warn about a risk, discloses the relevant scientific material to the FDA, and is rebuffed, then a later failure-to-warn claim is preempted. A state-law duty to give a warning that the FDA rejected is a duty to violate federal law—and therefore must give way to federal supremacy.

As explained, the FDA has final say over pharmaceutical labeling. *See supra* pp. 3–4. Thus, when the FDA, being fully informed of the available facts, rejects a label revision submitted through the PAS or CBE process, that is the end of the story. The manufacturer may not disregard the FDA's decision and forge ahead on its own. As a matter of law, the state cannot penalize the manufacturer for failure to warn of the health risk that the FDA refused to allow it to warn about. To use *Levine*'s language, the FDA obviously "*would not* have approved a change" to the label, 555 U.S. at 571 (emphasis added), where the FDA in fact *did not* approve a change to the label.

The federal regulatory framework confirms that the FDA's rejection of a request to add a warning is dispositive. After all, the FDA has a statutory duty to respond to new safety information that comes to

its attention: the agency must "promptly notify" the manufacturer of the information; "promptly review" the manufacturer's response; "initiate discussions to reach agreement on whether [or how] the labeling for the drug should be modified to reflect the new safety information"; and, if all else fails, "issue an order directing" the manufacturer "to make such a labeling change as [the FDA] deems appropriate to address the new safety information." 21 U.S.C. § 355(*o*)(4); *see supra* pp. 4–5. The FDA's regulations, too, obligate the agency to work with manufacturers to ensure that any medically appropriate warning makes it onto the drug's label. Thus, if a manufacturer's application contains "easily correctable deficiencies," the FDA will "make every reasonable effort to communicate [them] promptly to applicants" so that they may "correct [them] relatively early in the review process." 21 C.F.R. § 314.102(b). And if the "only deficiencies" in an application "concern editorial or similar minor deficiencies in the draft labeling," the FDA will "approv[e]" the request, "conditioned upon the applicant incorporating the specified labeling changes exactly as directed." *Id.* § 314.105(b).

In short, the FDA has statutory and regulatory duties to oversee drug labeling, respond to new information, and suggest revisions to proposed warnings that are supported by evidence but are (in the FDA's opinion) improperly worded. The FDA's outright *rejection* of a proposed warning by a complete response letter means the agency has concluded that a warning about that risk is not justified. And that turns any state-law failure-to-warn claim into an inappropriate—and preempted—

"second-guess[ing]" of the "FDA's decisionmaking." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 354 (2001) (Stevens, J., concurring in the judgment). That is, since federal law forbids giving a warning that the FDA believes is unjustified, any state-law duty to give such a warning is preempted.

C. Respondents' Failure-To-Warn Claims Are Preempted.

Under this legal framework, respondents' failure-to-warn claims must fail.

Proposed Warning. Merck "proposed to add language to the ... Warnings & Precautions ... section[] of [Fosamax's] label" to address "atypical femoral fractures." Pet.App.15a. Its cover letter to the FDA noted that the causal relationship between "low-energy subtrochanteric and/or proximal shaft fractures" and bisphosphonate use had not been established. Pet.App.15a. Yet Merck believed it was still "important to include an appropriate statement about them in the product label" to increase physician awareness and help physicians intervene early enough to "possibly prevent[] the progression to complete fracture." Pet.App.15a.

Merck's proposed warning did just that. Titled "Low-Energy Femoral Shaft Fracture," it told physicians that "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients." Pet.App.15a. Consistent with the reports Merck had received, Merck's proposal also noted that "[s]ome were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma." Pet.App.15a. It then recommended that

doctors evaluate patients with suspected fractures to rule out other possible causes (such as "extreme or increased exercise" or "glucocorticoid use," a known inhibitor of bone remodeling), and to consider "[i]nterruption of bisphosphonate therapy" after evaluating the pros and cons. Pet.App.16a.

FDA Rejection. The FDA rejected Merck's request to add a warning about atypical femoral fractures. The agency's complete response letter recognized that Merck sought to "add[] language to the PRECAUTIONS section and the ADVERSE REACTIONS, Post-Marketing Experience subsection ... to describe low-energy fractures at the subtrochanteric region of the femoral shaft." J.A.511 The FDA "agree[d] that atypical and subtrochanteric fractures should be added to the ADVERSE REACTIONS ... subsection[ ]" of the labels. J.A.511. But it concluded that Merck's "justification for the proposed PRECAUTIONS section language [was] inadequate." J.A.511. That was a flat, direct rejection, with no hint that the deficiencies were "easily correctable," 21 C.F.R. § 314.102(b), or could be cured by "editorial" changes, *id.* § 314.105(b).

Only after the task force report did the FDA conclude that it was appropriate to warn about the risk of atypical fractures potentially associated with bisphosphonate use. Before that time, the FDA believed that the literature was "conflicting," Pet.App.17a, and that there was no "clear connection" between the fractures and the drug, J.A.519. So the FDA called for "follow[ing] the recommendations in the [unrevised] drug label" while the agency "work[ed] closely with outside experts" to gather "more insight into this issue."

J.A.518–20; *see also* J.A.508 (FDA official's April 2009 email asking Merck to "hold off" on a warning so that FDA could study the issue further and "work with ... Merck to decide on language" for a warning "if it is warranted"). Only after an initial report from those "outside experts" did the FDA revisit its approach.

Disclosure of Evidence. Respondents cannot object that Merck hid the ball from the FDA. To the contrary, Merck told the FDA what it knew about the possible link between low-energy femoral fractures and bisphosphonate use. Merck "kept the FDA informed" of "scores of case studies, reports, and articles ... documenting possible connections" between the two. Pet.App.13a. A few months before Merck requested the label revisions, it "included over 30 pages of information" on the topic in its periodic safety update, and identified for the agency a host of "recent publications" about it. Pet. App. 14a. Indeed, in June 2008, the FDA stated that it was aware of the issue and had been tracking the safety signals. J.A.666. When the FDA asked for more information on the topic, Merck "promptly complied." There is thus no question—and respondents cannot now dispute, *see* S. Ct. R. 15.2—that Merck fully disclosed the possible connection between its drug and atypical femoral fractures. The FDA rejected its proposed warning with eyes wide open.

* * *

The FDA rejected Merck's request to warn about atypical femoral fractures. Because of that rejection, it was impossible for Merck to revise its label to conform to the state-law duties that respondents allege, without violating federal law in the process.

Respondents' claims—the ones that rest expressly on failure-to-warn theories, along with their disguised failure-to-warn claims that nominally rest on other theories—are therefore preempted.

II. THE THIRD CIRCUIT MISUNDERSTOOD *LEVINE* AND THE REGULATORY SCHEME.

The Third Circuit acknowledged that the FDA rejected Merck's proposed warning, but it held that respondents' claims must go to a jury anyway. According to the Court of Appeals, a jury "could find it less than highly probable" that the FDA would have rejected Merck's proposed warning had it been worded differently. Pet.App.56a–57a. In the Third Circuit's view, Merck must therefore prove to each jury in each individual case—by clear and convincing evidence, no less—that the FDA really meant what it said.

That analysis was wrong, because the Court of Appeals failed to understand the import of the FDA's action on Merck's actual proposal. Unlike in *Levine*, there is no need to resort to counterfactual analysis here; the answer is legally dictated by the course that the agency took in the real world. And, once that much is understood, the Third Circuit's succession of other errors—particularly its heightened standard of proof and its decision to send the question to a jury—become obvious.

A. The FDA's Real-World Action Here Eliminates the Need for Counterfactual Inquiry.

The Third Circuit treated the FDA's rejection of Merck's proposal as simply one piece of evidence for the jury to consider—along with "agency statements,

contemporaneous medical literature, ... and whatever intuitions the factfinder may have about administrative inertia," Pet.App.54a—in evaluating whether the FDA would have approved *any* warning about femoral fractures. The court concluded that a jury, weighing all of those considerations, could find that the FDA rejected Merck's proposal for purely semantic reasons, and thus that the FDA would have approved a differently worded warning about the same health risk. *See* Pet.App.56a, 62a–63a.

That was fundamentally wrong. It is true that, in *Levine*, this Court looked to "an existing fact record to predict the outcome of a hypothetical scenario." Pet.App.45a. But *Levine* considered a counterfactual world because it *had* to. There, "Wyeth ... d[id] not argue that it attempted to give the kind of warning required by the Vermont jury but was prohibited from doing so by the FDA." 555 U.S. at 572. Nor had the FDA given "more than passing attention to the issue." *Id.* Indeed, Wyeth did not even argue "that it supplied the FDA with an evaluation or analysis concerning the specific dangers posed by the IV-push method." *Id.* In such a case—without any agency action on the purported health risk in question—the preemption inquiry turns on whether the FDA "would ... have approved a change" had one been sought. *Id.* at 571.

By contrast, where the manufacturer *sought* a change—and a fully informed FDA *rejected* it—there is no reason for any counterfactual inquiry. The FDA's real-world action itself proves—with more than "clear evidence," *id.* at 571—that it would have been impossible to comply simultaneously with state and federal law. *See Dolin v. GlaxoSmithKline LLC*,

__ F. 3d __, 2018 WL 4001208, at *8 (7th Cir. Aug. 22, 2018) (distinguishing *Levine* from cases in which a fully informed FDA rejects a proposed warning after considering the risks).

The Third Circuit resisted that conclusion because it believed there might be space between what happened in the real world and what might have happened in an alternative one. On its view, the FDA might have rejected Merck's proposal because Merck used the supposedly imprecise term "stress fractures." Pet.App.67a. If so, Merck might have been able to change its label after all, in compliance with both state and federal law, if only it had used different terminology. That is, the FDA might have *agreed* with Merck that patients should be warned about atypical femoral fractures, but left the "ball ... in Merck's court" to rephrase its warning because "the burden ... to correct a drug label rests with the manufacturer, not the FDA." *Id.*

That reasoning—the crux of the Third Circuit's analysis—misunderstands the statutory and regulatory framework. As explained above, the law requires the FDA to work with manufacturers when it believes a label revision is warranted. *See supra* pp. 4–6. To be sure, the manufacturer "bears responsibility for the content of its label at all times"; it cannot do nothing in the face of newly emerging risks. Pet. App. 67a n.162 (quoting *Levine*, 555 U.S. at 570–71); *see also* 21 U.S.C. § 355(*o*)(4)(I). But if the FDA is fully aware of the new data—which, here, Merck provided in its PAS submission—the agency's own duties kick in. Those duties shed light on what an outright rejection by the agency means—that the FDA believes no revision is warranted. And the

FDA's own regulations—unmentioned by the Third Circuit—buttress that conclusion by clarifying that the agency does not reject otherwise-warranted warnings for semantic reasons. *See supra* pp. 5–6.

Any speculation that the FDA rejected Merck's proposal because of its *wording* would thus necessarily rest on the odious notion that the FDA ignored its own legal responsibilities and disregarded the public health. Indeed, the Third Circuit was admirably forthright on this front: it acknowledged that respondents' claims turn on whether the FDA chose to leave patients at risk rather than redline Merck's proposal. Pet.App.61a–62a.

That willingness to second-guess the FDA's conduct and speculate about agency lawlessness conflicts with established law. As a general matter, "a presumption of regularity attaches to the actions of Government agencies." *U.S. Postal Serv. v. Gregory*, 534 U.S. 1, 10 (2001). The Third Circuit was thus not free to impugn the FDA's "proper[] discharge[] of [its] duties" unless "clear evidence" showed that the agency had negligently carried them out. *United States v. Chem. Found.*, 272 U.S. 1, 14–15 (1926). There was no such evidence here: from first to last, the FDA's actions reflected its careful monitoring of the potential relationship between bisphosphonates and atypical femoral fractures. *See supra* pp. 7–16; *infra* pp. 49–50. Moreover, these are precisely the kinds of "conjectures" that *Mensing* (and preemption law more broadly) forbids. 564 U.S. at 621; *see also Buckman*, 531 U.S. at 353 (Stevens, J., concurring) (plaintiffs could not prove that the FDA would have disapproved of certain devices but for the alleged fraud on it, because the FDA "d[id] nothing to

remove the devices from the market, even though it [wa]s aware of the basis for the fraud allegations").

B. The Third Circuit's Approach Also Led It Astray in Other Ways.

In analyzing the hypothetical question of how the FDA would have responded to alternative warnings that Merck could have proposed, the Third Circuit also considered a series of meta-questions about that inquiry: Does it present a question of law or of fact? Should it be answered by a judge or jury? And by what standard of proof must Merck establish that the FDA would have rejected any such warning?

As explained above, the question here is what the FDA *actually did*, not what it *might have* done. And that moots the Third Circuit's analysis of these other questions. Interpretation of the FDA's actual agency action, after all, presents a classic question of law for a judge to decide, and evidentiary burdens of proof are irrelevant. Correcting the Third Circuit's basic legal framework thus also avoids the practical nightmare that, according to the Court of Appeals, necessarily followed: having hundreds of juries independently speculate about the reasons for the FDA's actions based on their own "intuitions" about medical science and administrative practice.

In any event, even if the Third Circuit were right that *Levine* mandates a counterfactual inquiry despite the FDA's real-world action on the purported health risk at issue, the court's answers to these other questions were mistaken. Preemption remains a question of law for a judge to decide, and *Levine* did not adopt a special "clear-and-convincing-evidence" standard for this unexceptional defense.

1. The Third Circuit expended great effort addressing whether its hypothetical question (what the FDA would have done) is a question of fact or law. *See* Pet.App.44a–54a. But the real issue here—the meaning and effect of what FDA *actually* did—is undoubtedly a legal one.

Questions about the meaning of an agency's actions are classic questions of law. For instance, in *B&B Hardware, Inc. v. Hargis Industries, Inc.*, this Court assessed the preclusive effect of a decision by the Trademark Trial and Appeal Board as a pure question of law. 135 S. Ct. 1293, 1302–1310 (2015). It has also assessed the preemptive effect of an agency's action (or inaction) as a question of law. *See, e.g.*, *Hillsborough Cty. v. Automated Med. Labs., Inc.*, 471 U.S. 707, 721 (1985); *Sprietsma v. Mercury Marine*, 537 U.S. 51, 64–68 (2002). Any question about the scope and import of the FDA's decision to reject Merck's PAS must be one of law, too.

Indeed, no one appears to disagree. The Third Circuit acknowledged that "determin[ing] the scope" of an agency's "formal regulatory pronouncement" is a legal task reserved for the court. Pet.App.53a n.135; *see also* Pet.App.52a (courts "determin[e] the ... legal effect ... of a writing"). It deemed the preemption inquiry to be factual only because it believed that it turned, not on the "legal effect [of the FDA's action] in the first instance," but on the "FDA's likely response to a differently worded proposal," Pet.App.52a—that is, on the counterfactual question rather than the real one.

Respondents were even more emphatic. After oral argument, the Third Circuit *sua sponte* asked for briefing on "the question of whether there is clear

evidence that the FDA would have approved a change to the drug's label is a question of fact or a question of law." Clerk's Letter at 1, No. 14-1900 (3d Cir., June 23, 2016). Respondents argued that, "[t]o the extent the determination depends on construction of final, written regulatory actions by the FDA, that is a [legal] task for the court." Plaintiffs-Appellants' Response Letter at 3, No. 14-1900 (3d Cir., Aug. 25, 2016). Respondents were right in that regard: this case presents a question of law because it turns on the meaning and effect of the FDA's action—namely, its decision to reject Merck's proposed warning. As explained, that agency action preempts respondents' failure-to-warn claims as a matter of law.

For similar reasons, the Third Circuit veered off-course in analyzing whether its hypothetical inquiry is for a judge or a jury. *See* Pet.App.38a–54a. To start, it is unclear why the Third Circuit even reached this question. Reasonable *juries* are entitled to no greater factual leeway than reasonable *judges* at summary judgment. So there was no need to determine the identity of the ultimate factfinder—only whether any genuine dispute of material fact existed.

In any event, the real questions here are purely legal ones about the meaning and effect of the FDA's action. "Bearing, as" they do, "the marks of ... 'question[s] of law,'" these questions are "one[s] for the judge," not for hundreds of juries. *Dennis v. United States*, 341 U.S. 494, 515 (1951). There is thus no need to swim through the Third Circuit's counterfactual quagmire, or to endorse a regime under which myriad juries in individual cases all

guess—based on "correspondence, agency statements, contemporaneous medical literature, ... and whatever intuitions the factfinder may have about administrative inertia," Pet.App.23a—about the FDA's position on whether the drug at issue should have carried the warning that plaintiffs claim state law requires.

The Third Circuit's counterfactual approach also led it astray in one final way. In *Levine*, the Court stated that, "absent clear evidence that the FDA would not have approved a change," it would "not conclude" that it was impossible for Wyeth to comply with federal and state law. 555 U.S. at 571. The Third Circuit held that this snippet of the Court's opinion requires drug manufacturers, in order to prevail on a preemption defense, to prove by "clear and convincing evidence" that the FDA would have rejected a proposed warning. Pet.App.37a.

This, too, was an unnecessary distraction. Standards of proof "refer to the degree of certainty by which the *factfinder* must be persuaded of a *factual* conclusion to find in favor of the party bearing the burden of persuasion." *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 100 n.4 (2011) (emphases added). These evidentiary standards simply do not apply to "questions of law" like those here. *See id.* at 114 (Breyer, J., concurring); *accord Concrete Pipe & Prods. of Cal., Inc. v. Constr. Laborers Pension Trust for S. Cal.*, 508 U.S. 602, 622 (1993) (explaining that "preponderance of the evidence" and "clear and convincing" are "standard[s] of proof" that direct the "factfinder" on how to "evaluate the raw evidence" in determining "the existence of a fact"). When a court construes a statute or regulation, or interprets the

import of agency action, it does so as a matter of law, and not by applying evidentiary burdens of proof.

2. Even if this really were a case about the hypothetical question of what the FDA would have done under different circumstances, the Court of Appeals erred by treating that as a factual question for a jury, and by reading *Levine* as imposing a heightened standard of proof.

The court appeared to believe that the task in such cases is to psychoanalyze FDA officials and speculate about what they would, in fact, have done. *E.g.*, Pet.App.48a. But that sort of unbounded inquiry would contravene the presumption that officials exercise their responsibilities faithfully in accordance with the law. *See Gregory*, 534 U.S. at 10. The real (hypothetical) question is thus whether the FDA, applying the law in light of the scientific record as it existed at a particular time, would have approved or rejected a proposed warning. That is best understood as a legal question for the court, because it involves interpreting statutes and regulations to determine whether a warning was required given the undisputed historical facts about the scientific data. *See Massachusetts v. EPA*, 549 U.S. 497, 533 (2007) (treating question whether the Clean Air Act required federal regulation of greenhouse gases as a question of law); Pet.App.46a n.122 (noting that "the historical facts are largely undisputed" here). Indeed, even if what the FDA would have done could be seen as a question of fact (or as a mixed question of law and fact), it should belong to a court: the Third Circuit gave no reason that a jury *must* decide this question, and there are many practical reasons for allocating it to a single

judge accustomed to interpreting and applying FDA regulations rather than to myriad juries unfamiliar with those tasks. *See, e.g.*, *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 388–91 (1996) (judges resolve claim construction in part because of their comparative advantage over jurors "unburdened by training in exegesis" and because of the need for "uniformity").

Last, the Third Circuit's demand for clear and convincing evidence was also incorrect, even if the inquiry were factual or evidentiary. In a "typical civil case involving a monetary dispute between private parties," the plaintiff's burden of proof is "a mere preponderance of the evidence," allowing the litigants to "share the risk of error in roughly equal fashion." *Addington v. Texas*, 441 U.S. 418, 423 (1979); *see, e.g.*, *Penn. State Police v. Suders*, 542 U.S. 129, 137 (2004) (affirmative defenses). This Court has departed from that standard only in rare circumstances, such as when Congress has told it to, *see, e.g.*, *Microsoft*, 564 U.S. at 113–14, or when some unusually compelling interest is involved—say, the importance of parental rights, *Santosky v. Kramer*, 455 U.S. 745, 769–70 (1982), or the dangers of involuntary commitment, *Addington*, 441 U.S. at 433. When lesser (but still weighty) concerns are at stake, the ordinary preponderance standard suffices. *See, e.g.*, *Rivera v. Minnich*, 483 U.S. 574, 579 (1987) (establishing paternity and its resulting obligations); *Steadman v. SEC*, 450 U.S. 91, 102 (1981) (permanently barring someone from investment advising).

Merck's preemption defense falls in the latter camp. To be sure, Plaintiffs allege serious injuries.

But most "monetary dispute[s] between private parties"—and all run-of-the-mill tort suits—involve allegations of serious harm, whether to someone's person, reputation, or business. That alone does not require either party in a slip-and-fall case to prove his position by clear and convincing evidence; such interests are not weighty enough to require one side to shoulder more of the risk of error.

The Third Circuit gave no good reason for its contrary conclusion. Without addressing these background principles, it parsed *Levine*'s single sentence about "clear evidence" as setting forth a "standard of proof," Pet. App. 35a–36a, and then reasoned that "clear evidence" is "synonymous with 'clear and convincing evidence,'" Pet.App.37a.

This result vividly shows why this Court's opinions are "not always to be parsed as though we were dealing with the language of a statute." *Reiter v. Sonotone Corp.*, 442 U.S. 330, 341 (1979). For starters, the Third Circuit was wrong in thinking that the Court has used terms like "clear evidence" consistently to demand heightened proof. Rather, this Court has noted that it has repeatedly used the phrase other than "in the strict evidentiary sense." *Block v. Cmty. Nutrition Inst.*, 467 U.S. 340, 350–51 (1984). *Levine*'s one-off reference to "clear evidence" is best understood to mean that, absent proof of what the FDA actually did or would have done, courts should not lightly assume that the FDA would have rejected a proposed warning. No more, no less.

Indeed, that reading of *Levine*'s reference to "clear evidence" is the only one that makes sense of the rest of the Court's opinion. *Levine* set forth *other*

formulations of the relevant preemption inquiry, like whether the "FDA would have prevented [the manufacturer] from adding a stronger warning." 555 U.S. at 573; *see id.* (whether it "was impossible for [the manufacturer] to comply with both federal and state requirements"). None of these formulations suggests any heightened proof requirement. Why read *Levine*'s lone reference to "clear evidence" to impose one when these other, equally important formulations do not?

The Third Circuit also reasoned that clear and convincing evidence is the proper standard because preemption "is a 'demanding defense' meant to represent a longstanding 'presumption against pre-emption.'" Pet.App.37a (quoting *Levine*, 555 U.S. at 565 n.3, 571–73). But "[i]mpossibility pre-emption is a demanding defense," *Levine*, 555 U.S. at 573, because the defendant must prove that it *could not have* complied with both state and federal law, not just that it would have been hard to do so. Given the inherent difficulty of that defense, there is no reason to tip the scales even more in the plaintiff's favor by skewing the usual burden of proof.

The supposed presumption against preemption is similarly irrelevant. No court has ever suggested that preemption defenses, across the board, must be proven by clear and convincing evidence. *See, e.g.*, *Boyle v. United Techs. Corp.*, 487 U.S. 500 (1988). And a presumption against preemption ignores the Supremacy Clause's *non obstante* provision—its declaration that federal law is supreme, "any Thing in the Constitution or Laws of any State to the Contrary notwithstanding," U.S. Const. art. VI, cl. 2. That language tells courts not to "distort federal law

to accommodate conflicting state law." *Mensing*, 564 U.S. at 623 (plurality op.); *see also* Caleb Nelson, *Preemption*, 86 Va. L. Rev. 225, 256 (2000) (*non obstante* provision "caution[s] against straining the meaning of a federal law to avoid a contradiction with state law"). That is exactly what a general presumption against preemption does. *See* Nelson, 86 Va. L. Rev. at 292–98.

In short, there is no good reason in law or logic to require drug manufacturers to prove what the FDA would have done with evidence as convincing as that needed to strip parents of their children.

* * *

This should have been an easy case. Respondents believe that state law required Merck to warn them about atypical femoral fractures—but Merck tried to do so and the FDA turned it back. There could be no clearer evidence that compliance with both state and federal law was impossible. The Third Circuit's labored contrary conclusion—based on its misreading of *Levine*, its misunderstanding of the FDA's role, and its misapplication of this Court's preemption precedents—must be reversed.

III. In Light of the FDA's Position Here, Merck Must Prevail.

Even if Merck were wrong about all of the above, it would still prevail here under the Third Circuit's framework. Merck already offered a host of evidence proving that the FDA would not have allowed Merck to add any warning about atypical femoral fractures. *See supra* pp. 7–16. But in addition to this evidence, Merck now has the very kind of "smoking gun" that the Third Circuit demanded: incontrovertible proof,

from the agency's own mouth, that it would not have authorized respondents' proposed warning until October 2010. Considering this new representation, no reasonable factfinder (judge *or* jury) could conclude that the agency would have permitted a warning about atypical femoral fractures at any earlier time. Merck is therefore entitled to summary judgment even under the Third Circuit's approach. *See* Fed. R. Civ. P. 56. Still, given the importance of these issues in pharmaceutical litigation nationwide, the Court should address the question presented despite the FDA's recent, case-specific comments.

1. The Third Circuit believed that a trial was necessary so that a jury could decide why the FDA rejected Merck's proposed warning—because it believed that no warning was warranted (in which case respondents' claims would be preempted), or because it disliked Merck's terminology (in which case an alternatively worded proposal might have been accepted, reconciling Merck's federal- and state-law duties). *See* Pet.App.62a–63a.

The FDA's certiorari-stage amicus brief now removes any possible doubt about why it rejected Merck's PAS: "FDA's May 2009 decision rejecting petitioner's proposal to modify Fosamax's Warnings and Precautions section to address atypical femoral fractures *was based on the agency's determination that the data was then insufficient to justify such a warning*." U.S. Cert. Br. 19 (emphasis added); *see also id.* at 22 ("FDA concluded in its Complete Response Letter that the justification for an enhanced warning was insufficient."). "It was only in October 2010—after an external task force had completed its report on the issue—that FDA came to

'believe that the information' about atypical femoral fractures should be added to the Warnings and Precautions section and therefore invoked Section 355(*o*)(4) to revise the labeling for Fosamax." U.S. Cert. Br. 22.

The FDA also explained that "[n]o sound basis ... exists for concluding that FDA determined in May 2009 that the data was sufficient to warrant a warning but that it rejected [Merck's] proposal because of [Merck's] proposed text." U.S. Cert. Br. 21. The complete response letter "rejected [Merck's] addition because the '*justification* for the proposed [Warnings and Precautions] section language [wa]s inadequate.'" U.S. Cert. Br. 20 (alterations and emphasis in U.S. Cert. Br.). And the FDA's statutory duties and regulatory framework prohibit it from engaging in the callous regulatory behavior that respondents imagine. "If a warning is warranted, FDA will attempt promptly to identify easily correctable deficiencies ... with the manufacturer in an iterative process." U.S. Cert. Br. 21. Had the FDA believed a warning were warranted, it would have worked with Merck to develop one, not least because "[s]ection 355(*o*)(4) would have *required*" the FDA to do so. U.S. Cert. Br. 22 (emphasis added); *see supra* pp. 4–5, 19–20.

Even under its erroneous approach, the Third Circuit already thought this was a close case. *See* Pet.App.62a–63a. It is now a slam dunk. Given the FDA's statement, "no reasonable juror could conclude that it is anything less than highly probable that the FDA would have rejected [respondents'] proposed atypical-fracture warning had Merck proposed it ... in September 2010." Pet.App.59a.

2. To credit respondents' account of the FDA's actions, this Court would have to ignore both ordinary principles of agency law and the record in this case.

An agency's explanation for its own action is given considerable weight in assessing preemption. In *Geier v. American Honda Motor Co.*, for example, the agency's explanation that it meant to preserve manufacturers' choices when it regulated passive-restraint systems "ma[d]e a difference" in determining whether to allow tort suits forcing manufacturers in a particular direction. 529 U.S. 861, 883 (2000). After all, "Congress ha[d] delegated to [the agency] authority to implement the statute; the subject matter [wa]s technical; and the relevant history and background [we]re complex and extensive." *Id.*; *see also Williamson v. Mazda Motor of Am., Inc.*, 562 U.S. 323, 335–36 (2011) (similarly deferring to the agency's views). Likewise here: if what matters is *why* the FDA rejected Merck's PAS and what the FDA would have done with a revised warning, it makes no sense to disregard the agency's own, direct answers to those questions.

Indeed, it would be particularly inappropriate to disregard the FDA's statements when, as here, the record contains no basis on which a factfinder could do so. The FDA's stated rationale for denying any warning before October 2010 is (at least) consistent with the FDA's complete response letter. *See supra* pp. 34–35. And it also finds conclusive support in the other evidence. The FDA's communications with Merck, its public statements, and its course of conduct all suggest what FDA now asserts: that only *after* the task force's report did FDA "c[ome] to

believe" that bisphosphonate manufacturers ought to warn about atypical femoral fractures. U.S. Cert. Br. 22. There is therefore no reason to disbelieve the FDA's representations to this Court.

Put another way, for this Court to find a genuine dispute as to what the FDA would have done with a rephrased warning, it would have to allow a rational factfinder to conclude either that the FDA misled the Court or that the agency misunderstood its own reasons for its actions. The former contradicts the presumption of regularity. *See supra* p. 39. And *both* options rest on sheer speculation, which is never enough to survive summary judgment, *see Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986), or to avoid preemption, *see Mensing*, 564 U.S. at 621.

Because no rational factfinder could conclude that FDA would have permitted Merck to warn about atypical femoral fractures prior to the task force's report, respondents' state-law failure-to-warn claims are preempted as a matter of law.

3. For these reasons, this Court should reverse the Third Circuit's judgment whether or not it agrees with that court's exposition of the law. In most preemption cases, however, the record will not include express FDA representations removing any ambiguity about the basis for its actions or how it would have responded to counterfactual scenarios. Manufacturers, after all, cannot compel the FDA to say what it would have done with a proposed label. *See United States ex rel. Touhy v. Regan*, 340 U.S. 462, 470 (1951) (agencies have "discretion to submit records voluntarily to the courts"); 21 C.F.R. §§ 20.1, 20.2. Considering the "importance of the pre-

emption issue" more broadly, *Levine*, 555 U.S. at 563, Merck therefore respectfully urges the Court to correct the Third Circuit's legal mistakes, not just reverse its Fosamax-specific judgment.

As Merck explained in its certiorari petition, lower courts applying *Levine* have erected unduly high hurdles to manufacturers' preemption defenses. Pet. 18–25. And a welter of litigation has ensued. *See* Cert. Br. of *Amicus Curiae* Product Liability Advisory Council, Inc., et al., in Support of Petitioner 9–12. Even manufacturers whose conduct is beyond reproach find themselves dragged through years of uncertain litigation. In *Dolin*, for example, the Seventh Circuit had to overturn a jury verdict in the plaintiff's favor even though the FDA had repeatedly rejected efforts to strengthen the drug's warning. __ F.3d __, 2018 WL 4001208; *see also Cerveny v. Aventis, Inc.*, 855 F.3d 1091 (10th Cir. 2017) (litigation even though FDA had "rejected a citizen petition containing arguments virtually identical" to plaintiffs'). Here, Merck faces over a thousand lawsuits even though it fully disclosed what it knew about Fosamax's risks and sought to warn about them.

These examples highlight the recurring nature of the Third Circuit's holdings, and "starkly illustrate[]" the "practical implications" of allowing its erroneous legal framework to stand. U.S. Cert. Br. 23. If manufacturers must face tort suits even when the FDA has made clear that no warning is necessary, they will continue to face an onslaught of troubling, coercive litigation. The Third Circuit's misbegotten legal framework should not stand.

CONCLUSION

The judgment below should be reversed.

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APPENDIX

APPENDIX A

21 U.S.C. § 355

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title. . . .

. . .

. . .

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; . . . or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the

conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence. The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for marketing approval of a drug.

. . .

(k) Records and reports; required information; regulations and orders; access to records

(1) In the case of any drug for which an approval of an application filed under subsection (b) or (j) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a

finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section. . . .

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

. . .

(o) Postmarket studies and clinical trials; labeling

(1) In general

A responsible person may not introduce or deliver for introduction into interstate commerce the new drug involved if the person is in violation of a requirement established under paragraph (3) or (4) with respect to the drug.

. . .

(4) Safety labeling changes requested by Secretary

(A) New safety information

If the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug, the Secretary shall promptly notify the responsible person or, if the same drug approved under subsection (b) is not currently marketed, the holder of an approved application under subsection (j).

(B) Response to notification

Following notification pursuant to subparagraph (A), the responsible person or the holder of the approved application under subsection (j) shall within 30 days--

(i) submit a supplement proposing changes to the approved labeling to reflect the new safety information, including changes to boxed warnings, contraindications, warnings, precautions, or adverse reactions; or

(ii) notify the Secretary that the responsible person or the holder of the approved application under subsection (j) does not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted.

(C) Review

Upon receipt of such supplement, the Secretary shall promptly review and act upon such supplement. If the Secretary disagrees with the proposed changes in the supplement or with the statement setting forth the reasons why no labeling change is necessary, the Secretary shall initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes.

(D) Discussions

Such discussions shall not extend for more than 30 days after the response to the notification under subparagraph (B), unless

the Secretary determines an extension of such discussion period is warranted.

(E) Order

Within 15 days of the conclusion of the discussions under subparagraph (D), the Secretary may issue an order directing the responsible person or the holder of the approved application under subsection (j) to make such a labeling change as the Secretary deems appropriate to address the new safety information. Within 15 days of such an order, the responsible person or the holder of the approved application under subsection (j) shall submit a supplement containing the labeling change.

(F) Dispute resolution

Within 5 days of receiving an order under subparagraph (E), the responsible person or the holder of the approved application under subsection (j) may appeal using dispute resolution procedures established by the Secretary in regulation and guidance.

. . .

. . .

. . .

21 CFR § 201.57

The requirements in this section apply only to prescription drug products described in § 201.56(b)(1) and must be implemented according to the schedule specified in § 201.56(c), except for the requirement in paragraph (c)(18) of this section to reprint any FDA–approved patient labeling at the end of prescription

drug labeling or accompany the prescription drug labeling, which must be implemented no later than June 30, 2007.

(a) Highlights of prescribing information. The following information must appear in all prescription drug labeling:

. . .

(6) Indications and usage. A concise statement of each of the product's indications, as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. If the product is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class in the following manner: "(Drug) is a (name of class) indicated for (indication(s))."

. . .

(9) Contraindications. A concise statement of each of the product's contraindications, as required under paragraph (c)(5) of this section, with any appropriate subheadings.

(10) Warnings and precautions. A concise summary of the most clinically significant information required under paragraph (c)(6) of this section, with any appropriate subheadings, including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm.

(11) Adverse reactions.

(i) A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., incidence rate). Adverse reactions important for other reasons (e.g., because they are serious or frequently lead to discontinuation or dosage adjustment) must not be repeated under this heading in Highlights if they are included elsewhere in Highlights (e.g., Warnings and Precautions, Contraindications).

. . .

. . .

(b) Full prescribing information: Contents. Contents must contain a list of each heading and subheading required in the full prescribing information under § 201.56(d)(1), if not omitted under § 201.56(d)(4), preceded by the identifying number required under § 201.56(d)(1). Contents must also contain any additional subheading(s) included in the full prescribing information preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(c) Full prescribing information. The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings, subheadings, and identifying numbers required under § 201.56(d)(1), unless omitted under § 201.56(d)(4). If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(1) Boxed warning. Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.

(2) Indications and usage. This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

(i) This section must include the following information when the conditions listed are applicable:

. . .

(F) If there are specific conditions that should be met before the drug is used on a long term basis (e.g., demonstration of responsiveness to the drug in a short term trial in a given patient), a statement of the conditions; or, if the indications for long

term use are different from those for short term use, a statement of the specific indications for each use.

. . .

(3) Dosage and administration.

(i) This section must state the recommended dose and, as appropriate:

. . .

(F) The usual duration of treatment when treatment duration should be limited,

. . .

. . .

. . .

(6) Warnings and precautions.

(i) General. This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section. In

accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

(ii) Other special care precautions. This section must contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (e.g., precautions not required under any other specific section or subsection).

. . .

(7) Adverse reactions. This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a

causal relationship between the drug and the occurrence of the adverse event.

(i) Listing of adverse reactions. This section must list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. The list or lists must be preceded by the information necessary to interpret the adverse reactions (e.g., for clinical trials, total number exposed, extent and nature of exposure).

(ii) Categorization of adverse reactions. Within a listing, adverse reactions must be categorized by body system, by severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency information cannot be reliably determined, adverse reactions must be listed in decreasing order of severity.

(A) Clinical trials experience. This section must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse reactions that occurred below the specified rate are included, they must be included in

a separate listing. If comparative rates of occurrence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined. For adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.

(B) Postmarketing experience. This section of the labeling must list the adverse reactions, as defined in paragraph (c)(7) of this section, that are identified from domestic and foreign spontaneous reports. This listing must be separate from the listing of adverse reactions identified in clinical trials.

. . .

(9) Use in specific populations. This section must contain the following subsections:

. . .

(v) 8.5 Geriatric use.

. . .

. . .

(d) Format requirements. All labeling information required under paragraphs (a), (b), and (c) of this section must be printed in accordance with the following specifications:

(1) All headings and subheadings required by paragraphs (a) and (c) of this section must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Reverse type is not permitted as a form of highlighting.

(2) A horizontal line must separate the information required by paragraphs (a), (b), and (c) of this section.

(3) The headings listed in paragraphs (a)(5) through (a)(13) of this section must be presented in the center of a horizontal line.

(4) If there are multiple subheadings listed under paragraphs (a)(4) through (a)(13) of this section, each subheading must be preceded by a bullet point.

(5) The labeling information required by paragraphs (a)(1) through (a)(4), (a)(11)(ii) through (a)(11)(iv), and (a)(14) of this section must be in bold print.

(6) The letter height or type size for all labeling information, headings, and subheadings set forth in paragraphs (a), (b), and (c) of this section must be a minimum of 8 points, except for labeling information that is on or within the package from

which the drug is to be dispensed, which must be a minimum of 6 points.

(7) The identifying numbers required by § 201.56(d) and paragraphs (c)(1) through (c)(18) of this section must be presented in bold print and must precede the heading or subheading by at least two square em's (i.e., two squares of the size of the letter "m" in 8 point type).

(8) The information required by paragraph (a) of this section, not including the information required under paragraph (a)(4) of this section, must be limited in length to an amount that, if printed in 2 columns on a standard sized piece of typing paper (8 1/2 by 11 inches), single spaced, in 8 point type with 1/2–inch margins on all sides and between columns, would fit on one-half of the page.

(9) Sections or subsections of labeling that are identified as containing recent major changes under paragraph (a)(5) of this section must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the new or modified text.

(10) For the information required by paragraph (b) of this section, each section heading must be in bold print. Each subheading within a section must be indented and not bolded.

21 CFR § 314.70

(a) Changes to an approved NDA.

(1)(i) Except as provided in paragraph (a)(1)(ii) of this section, the applicant must notify FDA about each change in each condition established in an

approved NDA beyond the variations already provided for in the NDA. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about the change in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the NDA under paragraph (d) of this section.

(ii) The submission and grant of a written request for an exception or alternative under § 201.26 of this chapter satisfies the applicable requirements in paragraphs (a) through (c) of this section. However, any grant of a request for an exception or alternative under § 201.26 of this chapter must be reported as part of the annual report to the NDA under paragraph (d) of this section.

(2) The NDA holder must assess the effects of the change before distributing a drug product made with a manufacturing change.

(3) Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented

in accordance with paragraphs (b) and (c) of this section.

(5) Except for a supplement providing for a change in the labeling, the applicant must include in each supplement and amendment to a supplement providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy has been provided in accordance with § 314.440(a)(4).

(6) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the submission.

(b) Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

(2) These changes include, but are not limited to:

. . .

(v) The following labeling changes:

(A) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

(B) If applicable, any change to a Medication Guide required under part 208

of this chapter, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter; and

(C) Any change to the information required by § 201.57(a) of this chapter, with the following exceptions that may be reported in an annual report under paragraph (d)(2)(x) of this section:

(1) Removal of a listed section(s) specified in § 201.57(a)(5) of this chapter; and

(2) Changes to the most recent revision date of the labeling as specified in § 201.57(a)(15) of this chapter.

. . .

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using a change under paragraph (b) of this section. Except for submissions under paragraph (e) of this section, the following information must be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The drug product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to assess the effects of the change;

(v) The data derived from such studies;

. . .

. . .

(c) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

. . .

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement—Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through

(b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved NDA may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

. . .

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of

a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental NDA, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

. . .

21 C.F.R. § 314.71

. . .

(b) All procedures and actions that apply to an application under § 314.50 also apply to supplements, except that the information required in the supplement is limited to that needed to support the change. A supplement is required to contain an archival copy and a review copy that include an application form and appropriate technical sections,

samples, and labeling; except that a supplement for a change other than a change in labeling is required also to contain a field copy.

(c) All procedures and actions that apply to applications under this part, including actions by applicants and the Food and Drug Administration, also apply to supplements except as specified otherwise in this part.

21 C.F.R. § 314.80

(a) Definitions. The following definitions of terms apply to this section:

> Adverse drug experience. Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.
>
> . . .

(b) Review of adverse drug experiences. Each applicant having an approved application under § 314.50 or, in the case of a 505(b)(2) application, an effective approved application, must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the

scientific literature, and unpublished scientific papers. Applicants are not required to resubmit to FDA adverse drug experience reports forwarded to the applicant by FDA; however, applicants must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section must also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

(c) Reporting requirements. The applicant must submit to FDA adverse drug experience information as described in this section. . . .

. . .

(k) Withdrawal of approval. If an applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

. . .

21 C.F.R. § 314.81

(a) Applicability. Each applicant shall make the reports for each of its approved applications and abbreviated applications required under this section and section 505(k) of the act.

(b) Reporting requirements. The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

. . .

(2) Annual report. The applicant shall submit each year within 60 days of the anniversary date

of U.S. approval of the application, two copies of the report to the FDA division responsible for reviewing the application. Each annual report is required to be accompanied by a completed transmittal Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use), and must include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval that ends on the U.S. anniversary date. The report is required to contain in the order listed:

(i) Summary. A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study. The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

. . .

(iii) Labeling.

(a) Currently used professional labeling, patient brochures or package inserts (if any), and a representative sample of the package labels.

(b) The content of labeling required under § 201.100(d)(3) of this chapter (i.e., the package insert or professional labeling), including all text, tables, and figures, must be submitted in electronic format. Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

(c) A summary of any changes in labeling that have been made since the last report listed by date in the order in which they were implemented, or if no changes, a statement of that fact.

. . .

(v) Nonclinical laboratory studies. Copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the

ingredients in the drug product. The applicant shall submit a copy of a published report if requested by FDA.

(vi) Clinical data.

(a) Published clinical trials of the drug (or abstracts of them), including clinical trials on safety and effectiveness; clinical trials on new uses; biopharmaceutic, pharmacokinetic, and clinical pharmacology studies; and reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant. Review articles, papers describing the use of the drug product in medical practice, papers and abstracts in which the drug is used as a research tool, promotional articles, press clippings, and papers that do not contain tabulations or summaries of original data should not be reported.

(b) Summaries of completed unpublished clinical trials, or prepublication manuscripts if available, conducted by, or otherwise obtained by, the applicant. Supporting information should not be reported. (A study is considered completed 1 year after it is concluded.)

(c) Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data

needed to ensure appropriate labeling for the pediatric population shall be included.

. . .

. . .

(d) Withdrawal of approval. If an applicant fails to make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

21 C.F.R. § 314.102

(a) General principles. During the course of reviewing an application or an abbreviated application, FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process. Such communication may take the form of telephone conversations, letters, or meetings, whichever is most appropriate to discuss the particular issue at hand. Communications shall be appropriately documented in the application in accordance with § 10.65 of this chapter. Further details on the procedures for communication between FDA and applicants are contained in a staff manual guide that is publicly available.

(b) Notification of easily correctable deficiencies. FDA reviewers shall make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application or an abbreviated application when those deficiencies are discovered, particularly deficiencies concerning chemistry, manufacturing, and controls issues. The agency will also inform applicants promptly of its need for more data or information or for technical changes in the application or the abbreviated application needed to

facilitate the agency's review. This early communication is intended to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed. Such early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application or abbreviated application by agency managers as well as reviewing staff. Instead, major scientific issues will ordinarily be addressed in a complete response letter.

. . .

21 C.F.R. § 314.105

. . .

(b) FDA will approve an NDA and issue the applicant an approval letter on the basis of draft labeling if the only deficiencies in the NDA concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.

. . .

21 C.F.R. § 314.110

(a) Complete response letter. FDA will send the applicant a complete response letter if the agency determines that we will not approve the application or abbreviated application in its present form for one or more of the reasons given in § 314.125 or § 314.127, respectively.

(1) Description of specific deficiencies. A complete response letter will describe all of the specific

deficiencies that the agency has identified in an application or abbreviated application, except as stated in paragraph (a)(3) of this section.

(2) Complete review of data. A complete response letter reflects FDA's complete review of the data submitted in an original application or abbreviated application (or, where appropriate, a resubmission) and any amendments that the agency has reviewed. The complete response letter will identify any amendments that the agency has not yet reviewed.

(3) Inadequate data. If FDA determines, after an application is filed or an abbreviated application is received, that the data submitted are inadequate to support approval, the agency might issue a complete response letter without first conducting required inspections and/or reviewing proposed product labeling.

(4) Recommendation of actions for approval. When possible, a complete response letter will recommend actions that the applicant might take to place the application or abbreviated application in condition for approval.

. . .

21 C.F.R. § 314.125

. . .

(b) FDA may refuse to approve an NDA for any of the following reasons, unless the requirement has been waived under § 314.90:

. . .

(6) The proposed labeling is false or misleading in any particular.

. . .

(8) The drug product's proposed labeling does not comply with the requirements for labels and labeling in part 201.

. . .

. . .

APPENDIX B

RESPONDENTS IN THIS PROCEEDING

Plaintiff	Appeal No.
Albrecht, Doris	14-1900
Molnar, Phyllis	14-2109
Molnar, William	14-2109
Gozdziak, Margaret	14-2110
Duke, Dolores	14-2111
Duke, Thomas	14-2111
Schultz, Susan	14-2112
Schultz, Russ	14-2112
Hines, Cynthia H.	14-2113
Hines, Robert N.	14-2113
Goodwin, Joan H.	14-2114
Moline, Barbara R.	14-2115
Moline, Ronald	14-2115
Wheeler, Kathryn K.	14-2117
Denker, Elayne	14-2118
Denker, Stephen	14-2118
Heaton, Nancy	14-2119
Bonne, Virginia	14-2120
Lefebvre, Alice	14-2121
Hogan, Marie	14-2122
Karch, Lillie	14-2123
Walraed, Susan	14-2124
Sullivan, J. Thomas	14-2124

Kolb, Lauren	14-2126
Kolb, Ralph	14-2126
Dematto, Mary E.	14-2127
Germino, Virginia Lee	14-2128
Chaires, Jeanette S.	14-2129
Salvatore, Sheila	14-2130
Collins, Lucille	14-2131
Miller, Betty	14-2132
Young, Marilyn	14-2133
Sunshine, Beverly	14-2134
Sunshine, Lawrence	14-2134
Sutton, Barbara	14-2135
Sutton, Charles	14-2135
Granato, Irene A.	14-2136
Granato, Samuel W.	14-2136
Graves, Barbara	14-2137
Brown, Elizabeth	14-2138
Brown, Robert	14-2138
Van, Mary Evelyn	14-2139
Zessin, Deloris M.	14-2140
Zessin, Robert F.	14-2140
Wirth, Carol	14-2141
Lyman, Patricia	14-2142
Foley, Peggy	14-2143
O'Brien, Molly	14-2144
O'Brien, Molly	14-2145
Evans, Laura	14-2146
Evans, William	14-2146
Krieg, Julia A.	14-2147
Krieg, Larry E.	14-2147
Cortez, Lorice	14-2148
Hardy, Shirley	14-2149
Marks, Martha	14-2150

Grassucci, Shirley	14-2151
Clougherty, Mary Patricia	14-2153
Edwards, Sybill	14-2154
Johnson, Susan	14-2155
Onaka, Eleanor	14-2156
Scott, Sylvia	14-2157
Whitt, Betty Jean	14-2158
Penigian, Jean	14-2159
Squires, Kathryn	14-2160
Collins, JoAnn	14-2161
Brogna, Loretta	14-2162
Brogna, Peter	14-2162
Hodge, Ellsworth	14-2163
Hodge, Helen	14-2163
Stark, Vivian	14-2164
Voss, Betty	14-2165
Voss, Eugene	14-2165
Schornick, Lori	14-2166
Panouis, Androniki	14-2167
Blackford, June	14-2168
Krakovitz, Pearl	14-2169
Pisarz, Josephine	14-2170
Pisarz, Walter	14-2170
Strominger, Betty	14-2171
Schick, Joan	14-2172
Schick, John Charles	14-2172
Chee, Paula	14-2173
Gribben, Angela	14-2174
Ourecky, Roberta M.	14-2175
Price, Carolyn	14-2176
Howe, Elaine F.	14-2177
Care, Margaret	14-2178
Hanel, Kannika	14-2179

Hanel, Joseph	14-2179
Standish, Debbie	14-2180
Standish, Kenneth	14-2180
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Radford, Shirley	14-2183
Poynor, Sherry	14-2184
Poynor, Bruce Raymond	14-2184
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Sontag, Marian	14-2186
Nelson, Edward	14-2187
Nelson, Gretchen Flint	14-2187
Haviland, Barbara	14-2188
Matney, Rosemary	14-2189
McGill, Barbara	14-2190
Schwalbe, Linda	14-2191
Schwalbe, Robert	14-2191
Nation, Karleen	14-2192
Misner, Anita	14-2193
Burke, Louise Findley	14-2194
Carter-Corcomb, Patty	14-2195
Messerli, Donna	14-2196
McKee, Eleanor	14-2197
McKee, Richard	14-2197
Mayes, Claudice	14-2198
Mayes, Claudice	14-2198
Joyce, Michael	14-2199
Hensley, Mary	14-2200
Degen, Patricia	14-2201
Mahan, Caroline	14-2202
Mistretta, Wilma	14-2203
Sorrentino, Theresa	14-2204

Tucker, Assunta	14-2205
Green, Mariella	14-2206
Green, Dewey	14-2206
Greenway, Ann P.	14-2207
Greenway, Ralph N.	14-2207
Ivey, Jane	14-2208
Driver, Virginia	14-2209
Driver, William	14-2209
Juth, Joann M.	14-2210
Juth, Bernard S.	14-2210
Buitron, Catherine	14-2211
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Wallis, Russell E.	14-2212
Wallis, Roseanne M.	14-2212
Carter, Ann D.	14-2213
McDaniel, Robert E.	14-2213
Murphy, Betty	14-2214
Murphy, Mark	14-2214
Sutton, Catrinia	14-2215
Duffy, Joan	14-2216
Pinkney, Lani	14-2217
Nagy, Norma	14-2218
Nagy, Charles W.	14-2218
Richardson, Lee	14-2219
Skinner, Leone	14-2220
Skinner, Marvin	14-2220
Steinert, Julie	14-2221
Steinert, Stephen Michael	14-2221
Lopes, Mary	14-2222
Lopes, Richard	14-2222
Shepherd, Madge	14-2223
Pappas, Diane	14-2224
Anderson, Barbara	14-2225

Nesbitt, Craig	14-2226
Coventry, Melinda	14-2227
Adams, Brenda	14-2228
Yancu, Milly	14-2229
Franklin, Suzane	14-2230
Davis, Patricia	14-2231
Foland, Bobbie	14-2232
Gerardo, Claudia	14-2233
Mueller, Eileen	14-2234
Held, Mary L.	14-2235
Held, Robert T.	14-2235
Weiss, Linda	14-2236
Weiss, Robert	14-2236
Hunt, Betty Burch	14-2237
Eisen, Ella	14-2239
Eisen, Herbert	14-2239
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Thomasson, Jack	14-2241
Schendle, Carolyn	14-2242
Schendle, James	14-2242
Hogan, Charlotte	14-2243
Hogan, Ronald	14-2243
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Baldridge, Charles A.	14-2244
McCabe, Doreen	14-2245
McCabe, John P.	14-2245
McCabe, Judith	14-2246
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Wilson, Sharon	14-2253
Stotts, Wilma	14-2254
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Grassel, Sara	14-2267
Halpern, Beverly	14-2268
Harvey, Robert	14-2269
Jones, Renae	14-2270
Singh, Priscilla	14-2271
Worthington, Renee	14-2272
Worthington, Norman	14-2272
Palmer, Richard	14-2273
James, Claudia	14-2274
James, Karol Dean	14-2274
Kozloski, Margaret	14-2275
Matthews, Roxie Mogler	14-2276
Newman, Lula	14-2277
Dirks, Susan	14-2278

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Madary, Roberta	14-2280
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Still, David	14-2290
Wheeler, Jo	14-2291
Smith, Richard	14-2292
Bucher, Rose	14-2293
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Goheen, Patty	14-2295
Powers, Peggy	14-2296
Powers, Mark	14-2296
Muller, Eleanor	14-2297
Muller, Alfred	14-2297
Lemley, Sheila	14-2298
Lemley, Lloyd	14-2298
Curry, Nellie	14-2299
Curry, Winford A.	14-2299

Thomas-Walsh, Theresa	14-2300
Walsh, Patrick	14-2300
Swanson, Nancy	14-2301
Swanson, Wayne	14-2301
Erickson, Doris	14-2302
Pearson, Linda	14-2303
Pearson, Harold	14-2303
Underhill, Mary Lee	14-2304
Underhill, Thomas	14-2304
Nord, Elayne Barbara	14-2305
Trense, Ronald V.	14-2305
Bryant, Jane	14-2306
Bryant, Alex	14-2306
Ciraolo, Joanna	14-2307
Savoy, Josephine	14-2308
Savoy, Harry	14-2308
Gentile, Emma	14-2309
Factor, Rosalyn Rena	14-2310
Walker, Sherry M.	14-2311
McCune, Bonnie L.	14-2312
Meldon, Virginia	14-2313
Greenberg, Carla A.	14-2314
Greenberg, Stephen M.	14-2314
Armstrong, Bobbie Jane K.	14-2315
Armstrong, John V. Sr.	14-2315
Garman, Rose Ann C.	14-2316
Garman, Dennis E.	14-2316
Goggin, Carol	14-2317
Goodman, Susan Jane	14-2318
Goodman, William L.	14-2318
Drouet, Renee	14-2319
Stroh, Kerry A.	14-2320

Medina, Laarni P.	14-2321
Whitman, Ethel	14-2322
Whitman, Glenn	14-2322
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D'Angelo, Henry F.	14-2323
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Harrow, Ronald A.	14-2325
Harrow, Ronnie M.	14-2325
Hardy, Yvette	14-2326
Lynn, Vivian	14-2327
Hill, Laura Lee	14-2328
Gitter, Blossom	14-2329
Clow, Edna	14-2330
Hulik, Linda	14-2331
Lyons, Janet	14-2332
Lyons, James	14-2332
Fitzpatrick, Nora	14-2333
Fitzpatrick, Edward	14-2333
Suehiro, Tokia	14-2334
Brown, Linton	14-2335
Brown, Leanna	14-2335
Seims, Marcie	14-2336
Seims, Gary	14-2336
Andrejasich, Anne	14-2337
Andrejasich, Frank	14-2337
Edwards, Sally	14-2338
Kakareka, Edith	14-2339
Jones, Denman	14-2340
Morris, Joyce	14-2341
Morris, Daniel	14-2341
Murphy, Cheryl	14-2342

Spires, Evelyn	14-2343
Davis, Anna M.	14-2345
Jefferies, Gail	14-2346
Ross, Betty Jo	14-2347
Jepson, Norma M.	14-2348
Fifer, Ladonna	14-2349
Moore, Marlene	14-2350
Moore, Joseph	14-2350
Bryant, Sharon	14-2351
Bishop, F. Richard	14-2352
Dharamsi, Kanta Manoj	14-2352
Dharamsi, Manoj	14-2352
Howe, Linda L.	14-2352
Howe, John N.	14-2352
Kohler, Elinor	14-2352
Peterson, Gonzalez Pura	14-2352
Peterson, Robert R.	14-2352
Bishop, Rosemary	14-2352
Burleson, Jacqueline R.	14-2354
Fenton, Carole M.	14-2355
Yost, Richard D.	14-2356
Yost, Marilyn P.	14-2356
Richard-Amato, Patricia	14-2357
Wang, Su-Mei	14-2358
Wang, Chan-Hsiung	14-2358
Zimmerman, Martha Farr	14-2359
Zimmerman, Blaine H.	14-2359
Flower, Gail A.	14-2360
Flower, James	14-2360
Cross, Katherine	14-2361
Mejia, Teresita	14-2362
Agrow, Rosalie	14-2363

Crook, Patricia	14-2364
Courville, Paula R.	14-2365
Bielecky, Margaret	14-2366
Wright, Judith	14-2367
Hayes, Mavis	14-2368
Hanson, Nelda	14-2369
Stencler, Roxanna	14-2370
Stencler, Peter	14-2370
Lowell, Sarah	14-2371
Lowell, Dan	14-2371
Collier, Marion	14-2372
Collier, Verne	14-2372
Waldrup, Roberta	14-2373
Waldrup, George	14-2373
Bohn, Edward J.	14-2375
Freay, Onnolee	14-2376
Sheehan, Yvonne T.	14-2377
Merrell, Preston	14-2378
Jones, Alice	14-2379
Fracaro, Fern	14-2380
McKelvey, Elizabeth	14-2381
Keaser, Barbara	14-2382
Brenner, Lois	14-2383
Azar, Bernice	14-2384
Hubbard, Linda	14-2385
Hubbard, John	14-2385
Arnold, Doris	14-2386
Halligan, Carla	14-2387
Frei, Miryam	14-2388
Besser, Deborah	14-2389
Dandridge, Earlene	14-2390
Dandridge, Kenneth Tyrone	14-2390

Weissberger, Kathryn	14-2391
Stone, Harriet	14-2392
Pustilnik, Jean	14-2393
Pickett, Theodore	14-2394
Bowden, Gregory	14-2395
Kniffen, Donna L.	14-2396
Kniffen, Donald L.	14-2396
Mayer, Christine G.	14-2397
Lynch, Kiersten	14-2398
Dunn, Lucille	14-2399
Nelson, Susan	14-2400
Nelson, James	14-2400
Lindenmeier, Janet	14-2401
Lindenmeier, Lester	14-2401
Frye, Barbara	14-2402
Frye, Eddie	14-2402
Sandfort, Irma	14-2403
Sandfort, Melvin	14-2403
Odum, Connie	14-2404
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No. 17-290

IN THE
Supreme Court of the United States

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

DORIS ALBRECHT, ET AL.,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Third Circuit

BRIEF FOR RESPONDENTS

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November 14, 2018

QUESTION PRESENTED

Respondents are more than 500 patients who suffered atypical femoral fractures caused by petitioner's drug, Fosamax. Respondents assert, among other claims, that petitioner failed to warn adequately of atypical femoral fractures. Although federal law permitted petitioner to add warnings to its drug label, petitioner never attempted to add a warning of atypical femoral fractures that would have satisfied its state-law duty. In 2009, the Food and Drug Administration ("FDA") sent a Complete Response Letter to petitioner declining to approve petitioner's proposal to warn of femur fractures that petitioner referred to as "stress fractures." Stress fractures are minor, incomplete fractures that are different from the severe atypical femoral fractures suffered by respondents. FDA explained that petitioner's "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." JA511.

The question presented is:

Whether the Third Circuit accurately assessed the record evidence in concluding that petitioner was not entitled to summary judgment on its preemption defense because petitioner had not shown beyond genuine dispute that FDA would have rejected an adequate warning about atypical femoral fractures.

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In *Wyeth v. Levine*, 555 U.S. 555 (2009), this Court held that failure-to-warn claims against brand-name drug manufacturers are not preempted because Congress enacted no applicable express preemption provision, such claims present no obstacle to federal purposes, and compliance with state law is not impossible because federal regulations permit manufacturers to update labeling approved by the Food and Drug Administration ("FDA"). As the Court held in *Levine* and reaffirmed in *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011), this rule against preemption gives way only where the manufacturer "show[s], by 'clear evidence,' that the FDA would have rescinded any change in the label and thereby demonstrate[s] that it would in fact have been impossible to do under federal law what state law required." *Id.* at 624 n.8 (quoting *Levine*, 555 U.S. at 571).

Petitioner Merck Sharp & Dohme Corp. ("Merck") challenges no aspect of that legal framework. This case concerns whether the factual record brings respondents' claims within the narrow, "clear evidence" exception. It does not. Merck's theory rests on mischaracterizations of specific FDA actions. Contrary to Merck's contentions, Merck never proposed the type of adequate warning of atypical femoral fractures sufficient under state law, and FDA never rejected such a warning. Rather, Merck proposed a warning focused on "stress fractures," which are common, minor fractures quite different from the debilitating atypical femoral fractures suffered by Fosamax users. In its Complete Response Letter, FDA rejected the stress-fracture warning because the literature did not support Merck's "[i]dentification of 'stress fractures'" or "[d]iscussion of the risk factors for stress fractures." JA511-12. FDA expressly invited Merck "to resubmit"

a revised warning that "addressed . . . the deficiencies listed." JA512. That FDA action did not preclude Merck from warning adequately of atypical femoral fractures.

Merck's preemption defense thus rests on speculation that FDA would have rescinded a warning that Merck never proposed. Merck bases that speculation on its informal communications with FDA, including its employee's notes purportedly describing her telephone call with an FDA official. The Third Circuit correctly determined that such equivocal evidence cannot support summary judgment. At most, it presents "the possibility of impossibility" that is "not enough" for preemption. *Mensing*, 564 U.S. at 624 n.8.

Merck now denigrates (at 40) as "moot[]" the question the government contended warranted certiorari: whether disputed factual issues regarding preemption should be submitted to judges or juries. Merck is right that the procedural issues addressed by the Third Circuit (the allocation of fact-finding responsibilities and the standard of proof) are irrelevant to whether the Third Circuit's holding reversing summary judgment in Merck's favor should be affirmed. If the Court nonetheless addresses those procedural issues, it should affirm the Third Circuit's handling of those issues and follow the generally applicable rule that the jury decides disputed factual questions.

STATEMENT

A. Statutory And Regulatory Background

1. Since Congress enacted the Federal Food, Drug, and Cosmetic Act ("FDCA") in 1938, FDA has regulated prescription drugs and their labeling. Congress passed the FDCA amidst a background history of state-law tort suits against drug manufacturers, including failure-to-warn claims for dangerous side effects.[1] Congress declined to insert a federal cause of action in the FDCA, determining "that widely available state rights of action provided appropriate relief for injured consumers." *Levine*, 555 U.S. at 574.

Although legislation and FDA regulations have evolved over the past eight decades, two features of the regulatory regime have remained constant. First, "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Id.* at 570-71.

Second, even as Congress has "enlarged the FDA's powers," it has "t[a]k[en] care to preserve state law." *Id.* at 567. Thus, in 1962, when Congress amended the FDCA to require the manufacturer to prove safety and effectiveness, Congress "added a saving clause, indicating that a provision of state law would only be invalidated upon a 'direct and positive conflict' with the FDCA." *Id.* (quoting Drug Amendments of 1968,

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[1] *See, e.g., Halloran v. Parke, Davis & Co.*, 280 N.Y.S. 58, 59 (App. Div. 1935) (per curiam); *Fisher v. Golladay*, 38 Mo. App. 531, 536-43 (1889); *Blood Balm Co. v. Cooper*, 10 S.E. 118, 119 (Ga. 1889); *Thomas v. Winchester*, 6 N.Y. 397, 407-10 (1852); *Fleet v. Hollenkemp*, 52 Ky. (13 B. Mon.) 219, 225-29 (1852).

Pub. L. No. 87-781, § 202, 76 Stat. 780, 793). In addition, "when Congress enacted an express pre-emption provision for medical devices in 1976, it declined to enact such a provision for prescription drugs." *Id.* (citation omitted). To this day, there is no express preemption provision relating to prescription drugs.

2. The FDCA generally forbids the sale of a prescription drug in interstate commerce unless it has been approved by FDA. 21 U.S.C. § 355(a). A manufacturer seeking approval of a brand-name drug must file a new drug application ("NDA") with FDA.[2] An NDA includes proposed labeling. *Id.* § 355(b)(1)(F).

Nothing in the FDCA prohibits a manufacturer from changing the label of a brand-name drug after FDA approval, so long as the label does not render the drug "misbranded." *See id.* §§ 331(a), 352(a) (drug is misbranded "[i]f its labeling is false or misleading in any particular"). Changing an approved label does not, on its own, render a drug misbranded, and this Court has found it "difficult to accept" that "FDA would bring an enforcement action against a manufacturer for strengthening a warning." *Levine*, 555 U.S. at 570.

FDA regulations long have expressly authorized brand-name drug manufacturers to revise labeling unilaterally to strengthen warning language. FDA first promulgated such a regulation in 1965. *See* 30 Fed. Reg. 993, 993-94 (Jan. 30, 1965); 21 C.F.R. § 130.9(d)(1), (e) (1966). Under the current changes being effected ("CBE") regulation, a manufacturer may make "[c]hanges in the labeling to reflect newly acquired information" without prior FDA approval,

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[2] Fosamax is a brand-name drug. Separate statutory and regulatory provisions, not at issue here, govern approval and labeling of generic drugs. *See generally Mensing*, 564 U.S. at 612-17.

if the change is "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under [21 C.F.R.] § 201.57(c)." 21 C.F.R. § 314.70(c)(6)(iii)(A). "Newly acquired information" includes "data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses)." *Id.* § 314.3(b). A manufacturer making such a label change must submit a supplement to FDA regarding the change; if FDA disapproves the CBE supplement, "it may order the manufacturer to cease distribution of the drug product(s) made with the . . . change." *Id.* § 314.70(c)(6)(iii), (c)(7). A manufacturer also can apply for FDA approval to update the label through a "Prior Approval Supplement" ("PAS"), which involves prior approval by FDA. *Id.* § 314.70(b)(2)(v)(A).

3. FDA regulations establish the format of drug labeling. Two sections of the label are relevant here: "Adverse Reactions," and "Warnings and Precautions." The Adverse Reactions section includes a listing of all "undesirable effect[s], reasonably associated with use of a drug." 21 C.F.R. § 201.57(c)(7).[3] A manufacturer must list an adverse reaction if "there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse

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[3] Section 201.57 describes labeling requirements for drugs approved on or after June 30, 2001. 21 C.F.R. § 201.56(b)(1). Somewhat different requirements apply to older drugs. *Id.* §§ 201.56(e), 201.80. The three Fosamax drugs implicated in respondents' suits were approved in 1995, 2003, and 2005; the parties and the government agree the labeling requirements for older and newer drugs do not differ in any respect material here, and accordingly address the labeling requirements for newer drugs in § 201.57. *See* U.S. Br. 2 n.1.

event." *Id.* The Warnings and Precautions section describes "clinically significant adverse reactions," "limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification)." *Id.* § 201.57(c)(6)(i). This section "must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." *Id.* Since 2008, those standards also have applied to warnings added through a CBE supplement. *Id.* § 314.70(c)(6)(iii)(A).

If FDA "determines that [it] will not approve" either an NDA or a labeling supplement "in its present form," it will "send the applicant a complete response letter." *Id.* § 314.110(a). The complete response letter "will describe all of the specific deficiencies that the agency has identified in an application." *Id.* § 314.110(a)(1). The purpose of a complete response letter is "to inform[] sponsors of changes that must be made before an application can be approved, with no implication as to the ultimate approvability of the application." 73 Fed. Reg. 39,588, 39,589 (July 10, 2008). FDA provides three options to an applicant who has received a complete response letter: (1) "[r]esubmit the application . . . , addressing all deficiencies identified in the complete response letter"; (2) "[w]ithdraw the application"; or (3) request a hearing at which FDA will make a final determination whether to approve or reject the application. 21 C.F.R. § 314.110(b).

4. Until the Food and Drug Administration Amendments Act of 2007 ("FDAAA"), FDA lacked authority to mandate that manufacturers change prescription drug labels. *See Levine*, 555 U.S. at 571.

The FDAAA gave FDA authority to initiate a process to mandate label changes if FDA "becomes aware of new safety information" that FDA "believes should be included in the labeling of the drug." 21 U.S.C. § 355(*o*)(4)(A). Congress included a "[r]ule of construction" that "[t]his paragraph shall not be construed to affect the responsibility of the [manufacturer] to maintain its label in accordance with existing requirements, including . . . [21 C.F.R. §] 314.70." *Id.* § 355(*o*)(4)(I).

B. Factual History

1. Respondents are more than 500 individuals (or their spouses or representatives) from roughly 45 States who allege that they suffered an atypical femoral fracture ("AFF") caused by their use of Fosamax, a brand-name osteoporosis drug manufactured by petitioner. Pet.App.75a-95a; Resp. C.A. Br. Jurisdictional App. Respondents suffered their injuries between January 1999 and September 2010. MDL Dkt. 2857-2.

An atypical femoral fracture is a debilitating fracture in which the thigh bone, or femur, often breaks in two. JA288-89; *see also* JA290, 336, 388, 410, 662 (x-rays). Atypical femoral fractures generally occur in the proximal (or upper) third of the femoral shaft, and may occur in the subtrochanteric region, which is just below the two protuberances (called trochanters) at the top of the femur. JA288-92. Atypical femoral fractures are low-energy fractures, meaning they are associated with no trauma or minimal trauma. JA292. They generally have a transverse or short oblique configuration, meaning the fracture cuts across the bone, perpendicular to the femoral shaft (or slightly slanted). *Id.*

2. FDA approved Fosamax in 1995 to treat osteoporosis and in 1997 to prevent osteoporosis; post-menopausal women most commonly use the drug. Pet.App.5a, 12a-13a. Fosamax's scientific name is "alendronate sodium" (sometimes shortened to "alendronate"), and Fosamax belongs to a class of drugs called bisphosphonates that are commonly used to treat osteoporosis. JA192 (Fosamax Jan. 2011 label).[4]

Human bones constantly undergo a rebuilding process called remodeling or turnover. JA102 (Burr Decl. ¶ 13). In the remodeling process, bone breaks down (resorption) and new bone cells form at that same location (formation). *Id.* Bone remodeling repairs and removes microcracks, which are small fractures that accumulate through normal activity. *Id.* In post-menopausal women, the rate of resorption often exceeds that of formation, leading to bone loss. *Id.*

Fosamax reduces bone resorption by inhibiting the activity of bone-resorbing cells called osteoclasts. JA197 (Fosamax Jan. 2011 label). Fosamax "ultimately reduce[s]" bone formation because it inhibits bone resorption, and "bone resorption and formation are coupled during bone turnover." JA198. According to the expert report of Dr. David Burr, one of the world's leading orthopedic scientists, the "significant reduction in bone turnover" can "increase bone mass, but numerous studies demonstrate that it also creates older bone and negatively affects bone tissue quality."

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[4] In 2003 and 2005, respectively, FDA approved variants of Fosamax in an oral solution and in a tablet combined with Vitamin D called "Fosamax Plus D." *See* U.S. Br. 2 n.1. No party contends the relevant labeling history or preemption analysis differs with any of the three Fosamax variants. This brief uses "Fosamax" to refer collectively to all three Fosamax products.

JA102-03 (Burr Decl. ¶¶ 14-15). Long-term bisphosphonate use "affect[s] the material properties of bone over time by reducing bone toughness and its ability to repair microcracks." JA144 (*id.* ¶ 84). Consequently, long-term Fosamax users may suffer incomplete fractures that "continue to grow until complete fracture of the bone." JA144-45 (*id.* ¶ 84); Pet.App.6a.

The type of femoral fractures associated with Fosamax use are called atypical femoral fractures, or AFFs. JA101 (Burr Decl. ¶ 12). Because of the surge in these previously rare fractures among Fosamax patients, by 2002, leading orthopedic surgeons dubbed them "Fosamax Fracture[s]." JA126 (*id.* ¶ 52); JA448; C.A.App.1254.

3. Evidence connecting Fosamax and other bisphosphonates to atypical femoral fractures emerged over time. In internal discussions in 1990 and 1991, when Fosamax was undergoing early clinical trials, Merck scientists expressed concern that Fosamax could inhibit bone remodeling to such a degree that "inadequate repair may take place" and "micro-fractures would not heal." JA111-13 (Burr Decl. ¶¶ 25-28); C.A.App.1180, 2462-63. A 1995 Merck report on a Fosamax clinical trial demonstrated significant reduction in bone turnover. C.A.App.2548-50.

In 1999, Merck began receiving adverse event reports indicating long-term Fosamax users were suffering atypical femoral fractures. JA122-25 (Burr Decl. ¶¶ 45-50) (describing reports). In 2005, Merck received a report from orthopedic surgeon Dr. Joseph Lane of "25 patients with long bone fractures that . . . have taken Fosamax . . . for a long time," noting that in his hospital they call such a fracture the "Fosamax

Fracture." JA126 (*id.* ¶ 52) (last alteration in original); *see* JA448. Other orthopedic physicians similarly raised concerns about fractures resulting from long-term Fosamax use. JA462-63, 649-51. Also in 2005, Merck performed a statistical data-mining analysis of Fosamax adverse event reports, concluding that these reports revealed a statistically significant incidence of femur fractures beginning in September 2003. C.A.App.1272-73, 1443. Respondents' biostatistician expert David Madigan confirmed that FDA's adverse event database for Fosamax showed a statistically significant signal in 2005 of a relationship between Fosamax and femur fractures. JA189-91. In 2006, a Merck regulatory-affairs employee in Singapore reported learning of eight cases of atypical femoral fractures suffered by long-term Fosamax users and suggested that they "might be a signal for a label update." JA452, 455-56.

Scholarly articles and case studies documented the connection between bisphosphonates and atypical femoral fractures. A 2004 article studied several Fosamax patients who had suffered atypical femoral fractures and concluded "[o]ur findings raise the possibility that severe suppression of bone turnover may develop during long-term alendronate therapy, resulting in increased susceptibility to, and delayed healing of, nonspinal fractures." JA416. A 2008 article studied 25 Fosamax users who had suffered atypical femoral fractures, concluding that such fractures were "associated with alendronate use." JA386.[5] As the Third Circuit summarized, "[b]etween 1995 and 2010, scores of case studies, reports, and articles were

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[5] *See generally* JA106-10, 116-22 (Burr Decl. ¶¶ 19-24, 35-44) (describing numerous studies connecting Fosamax or bisphosphonates generally to weakened bone or atypical femoral fractures).

published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures." Pet.App.13a.

Fosamax not only carries significant risks, but also has not been shown to reduce fractures for many users, including patients without osteoporosis or a preexisting vertebral fracture. JA179 (Furberg Decl. ¶ 64). Fosamax is commonly prescribed to patients who have below-average bone density but not osteoporosis. In one of Merck's clinical trials of Fosamax use by such patients, the Fosamax-treatment group suffered more fractures than the placebo group. JA167 (*id.* ¶ 40). Merck's Director of Clinical Research acknowledged in sworn testimony that "[t]here's no evidence" Fosamax "reduces the risk of fracture in women who don't have osteoporosis." JA460 (Santora Dep. 796). Even among patients with osteoporosis, there is no demonstrated fracture-reduction benefit beyond three years of use. JA179 (Furberg Decl. ¶ 66).

4. Fosamax's label contained no mention of femur fractures from its approval in 1995 through 2008. Pet.App.12a-14a. In June 2008, FDA informed petitioner that it was "aware of reports" of bisphosphonate users suffering atypical femoral fractures and was "concerned about this developing safety signal." JA280.

In September 2008, petitioner submitted a PAS application to FDA to add mentions of fractures to both the Adverse Reactions and the Warnings and Precautions sections of the Fosamax label. JA669. Merck proposed adding a reference to "low-energy femoral shaft fracture" in the Adverse Reactions section and to cross-reference a longer discussion in the Warnings and Precautions section. JA728. In the

Warnings and Precautions section, Merck proposed to add the following language:

> *Low-Energy Femoral Shaft Fracture*
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. ***Some were stress fractures*** (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area often associated with ***imaging features of stress fracture*** weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and ***stress fractures with similar clinical features*** also have occurred in patients not treated with bisphosphonate. ***Patients with suspected stress fractures*** should be evaluated including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, ***previous stress fracture***, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse) and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in ***patients with stress fractures*** should be considered pending evaluation of the patient, based on individual benefit/risk assessment.

JA707 (emphases added).

Every sentence after the first sentence referred to the femur fractures as "stress fractures." A stress fracture is different from an atypical femoral fracture. A stress fracture is "an incomplete fracture of a long bone," the vast majority of which "never progress to a full and complete fracture," and which is generally treated "by prescribing rest or inactivity in the

affected bone." JA144 (Burr Decl. ¶ 83). By contrast, atypical femoral fractures often progress to a "completed subtrochanteric fracture" of the femur and are "much more significant than 'garden-variety' stress fractures, which usually heal uneventfully with simple rest and without full fracture." JA145-46 (*id.* ¶ 86). As FDA explained in 2010, characterizing atypical femoral fractures as "stress fractures" would "contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use" because, "for most practitioners, the term 'stress fracture' represents a minor fracture." JA566. Merck also acknowledged that "most of the stress fractures general physicians have seen are associated with repetitive stress injury related to exercise (e.g., running) in younger adults, and that this type of stress fracture generally heals well with rest." C.A.App.1573.

Figure 1 is an x-ray of an atypical femoral fracture suffered by an alendronate user; Figure 2 is an x-ray of a stress fracture of the femoral shaft.

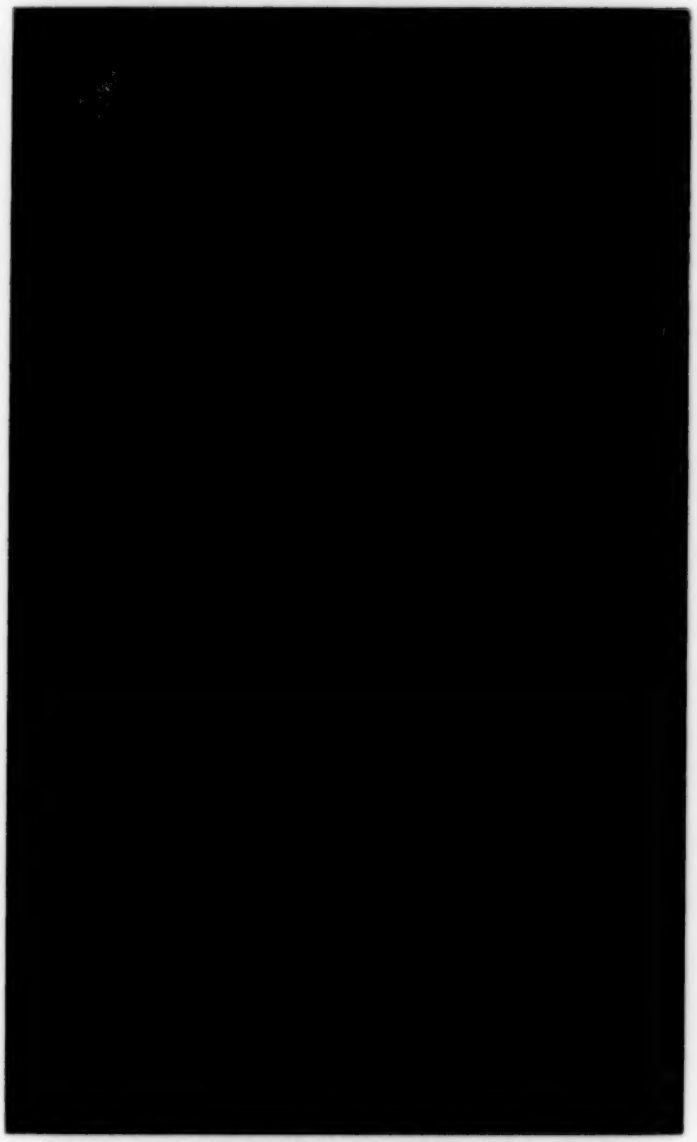

Figure 1: atypical femoral fracture suffered by Fosamax user[6]

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[6] JA388.

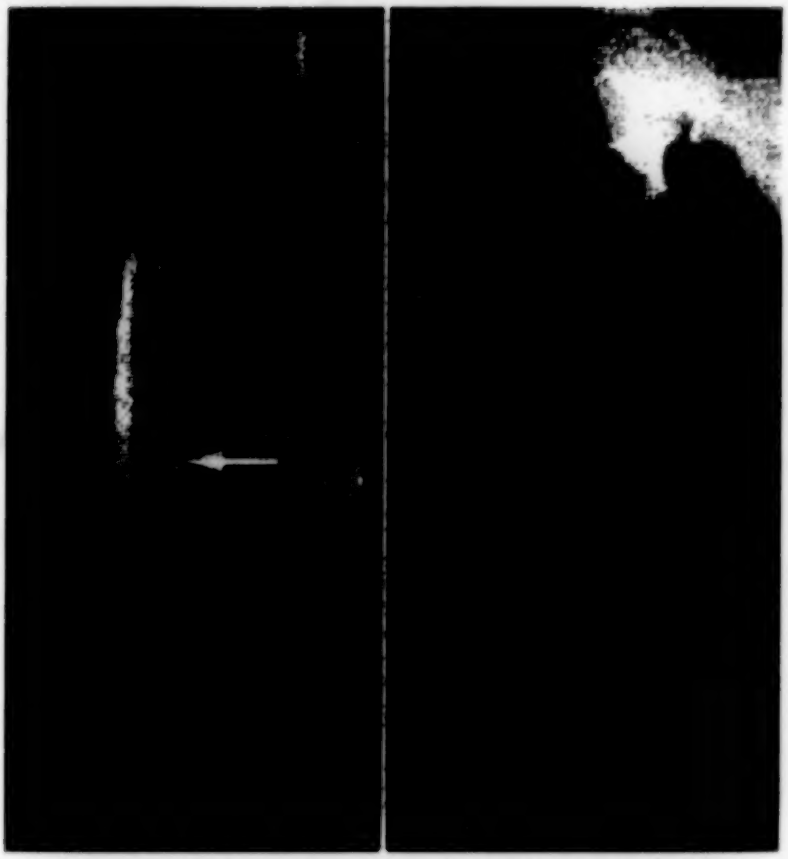

Figure 2: stress fracture of the femoral shaft[7]

On May 22, 2009, FDA sent Merck a "Complete Response" letter by Dr. Scott Monroe, granting in part and denying in part petitioner's application. JA510-13. FDA approved the addition of "low energy femoral shaft and subtrochanteric fractures" to the Adverse Reactions section, JA512, reflecting the conclusion "there is some basis to believe" Fosamax causes those

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[7] Alan Ivkovic et al., *Stress fractures of the femoral shaft in athletes: a new treatment algorithm*, 40 Br. J. Sporta. Med. 518 (2006), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2465093/.

fractures, 21 C.F.R. § 201.57(c)(7). Regarding the proposed Warnings and Precautions language, FDA responded:

> [Y]our justification for the proposed **PRECAUTIONS** section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting.

JA511-12. FDA invited Merck to "resubmit" its application and to "fully address all the deficiencies listed." JA512.

In June 2009, Merck withdrew its PAS application and added the approved femur-fracture language to the Adverse Reactions section of the Fosamax label through a CBE supplement, but did not add any reference to femur fractures in the Warnings and Precautions section. JA274, 279, 657. Merck has submitted no evidence it took any action to resubmit its application or worked with FDA on atypical-femoral-fracture language for the Warnings and Precautions section at that time.

5. On March 10, 2010, FDA issued a drug-safety communication that it was "working closely with outside experts," including a Task Force of the American Society for Bone and Mineral Research ("ASBMR Task Force"), "to gather additional information that may provide more insight" into the connection between bisphosphonates and atypical femoral fractures. JA519-20.

On September 14, 2010, the ASBMR Task Force published a report describing the features of atypical

femoral fractures, JA288-93, and concluding that "there is evidence of a relationship between long-term [bisphosphonate] use and a specific type of subtrochanteric and femoral shaft fracture," JA355. According to Dr. Burr, a principal author of the report, the Task Force did not conduct any additional clinical research; it simply "review[ed]" "the currently available information," most of which was available before May 2009. JA133-34 (¶ 62).

On October 13, 2010, FDA announced it would require all bisphosphonate manufacturers to warn of atypical femoral fractures. JA246. That same day, FDA proposed specific language for the Fosamax label, describing "[a]typical femoral fractures" in the Warnings and Precautions section. JA528-29. FDA explained that, although "it is not clear if bisphosphonates are the cause, . . . these atypical fractures may be related to long-term bisphosphonate use." JA247. Merck proposed revised language that added five references to "stress fractures," including the language relating to risk factors for stress fractures that FDA had rejected in 2009. JA606-07. FDA sent Merck a redline substantially rewriting Merck's proposal; FDA struck out each reference to stress fractures and revised the language so that it was nearly identical to what FDA originally proposed. *Id.*; *compare* JA528-29 (initial FDA proposal). FDA explained that "the term 'stress fracture' was considered and was not accepted" because, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use." JA566.

In January 2011, Merck added a three-paragraph discussion of atypical femoral fractures to the

Warnings and Precautions section of the Fosamax label, which remains on the label today. JA223-24. With the heading "*Atypical Subtrochanteric and Diaphyseal Femoral Fractures*," the language states that "[a]typical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients." JA223. It describes atypical femoral fractures as being "transverse or short oblique in orientation" and advises that patients with symptoms of an atypical femoral fracture should consider "[i]nterruption of bisphosphonate therapy." JA223-24. The warning now refers to the fractures five times as "atypical" without using the term "stress fracture." *Id.*

C. Procedural History

1. In May 2011, the Judicial Panel on Multidistrict Litigation ordered 36 then-pending actions involving claims that Fosamax or its generic equivalents caused femur fractures to be centralized for consolidated pretrial proceedings in the District of New Jersey in a multi-district litigation ("MDL"). *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig. (No. II)*, 787 F. Supp. 2d 1355 (J.P.M.L. 2011). Respondents' actions were filed in or transferred to the Fosamax MDL. Pet.App.75a-95a.

Although the complaints differ in their particularities, respondents generally alleged that Fosamax caused them to suffer atypical femoral fractures and that Merck is liable for respondents' injuries because, among other reasons, Merck failed to warn about atypical femoral fractures in a way that would apprise respondents or their physicians of the risks. For example, Lorice Cortez alleged that she took Fosamax from 1999 through 2010 and, "[a]s a result of using . . . Fosamax," she "suffered from a fracture of her left

femur" on August 31, 2009, at age 70. Cortez Compl.[8] ¶¶ 50-51, 54. "[W]hile turning to unlock the front door of her house, Mrs. Cortez[] heard a popping sound then she suddenly felt her left leg give out from beneath her." Braniff Decl.[9] ¶ 144. Her fracture required surgery, in which her leg was repaired by a rod and screws. Cortez Compl. ¶ 55. She alleged Merck "failed to change" its labeling "to warn of the potential for femur fractures" and "did not provide adequate warnings . . . about the increased risk of serious adverse events." *Id.* ¶¶ 39, 46. She explained she "would not have used Fosamax for so many years had Defendant properly disclosed the risks associated with its long-term use." *Id.* ¶ 58.[10]

2. In April 2013, the district court held the first bellwether trial in a case brought by Bernadette Glynn and her husband (who are not respondents here). Pet.App.24a-25a; C.A.App.2093-94. No respondent was a party to the *Glynn* action. Merck had filed motions for summary judgment and judgment as a matter of law on preemption, but the court reserved judgment on those motions and submitted the Glynns' failure-to-warn claim to the jury. Pet.App.163a-164a. On April 29, 2013, the jury found against the Glynns, deciding in a special verdict that Ms. Glynn failed to prove "she experienced an atypical femur fracture in April 2009." JA45.

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[8] Compl., *Cortez v. Merck Sharp & Dohme Corp.*, No. 3:11-cv-05025-FLW-LHG, Dkt. #1 (D.N.J. Aug. 31, 2011).

[9] MDL Dkt. 2946, Ex. A.

[10] *See also, e.g.*, JA40-42 (Knopick Compl. ¶¶ 41, 43, 57, 59); JA26-27, 29, 32-33 (Steves Compl. ¶¶ 62, 73, 83, 123, 125); JA639-40, 642 (Jones Compl. ¶¶ 61, 64, 66, 73).

On June 27, 2013, after the jury's defense verdict, the district court issued an unusual advisory opinion, concluding that federal law preempted the Glynns' claims. Pet.App.153a-174a. The court reasoned that FDA's rejection of Merck's proposed "stress fracture" warning language in the Warnings and Precautions section in 2009 provided "'clear evidence'" that Merck could not have added any warning of atypical femoral fractures to the Fosamax label. Pet.App.168a-174a (quoting *Levine*, 555 U.S. at 571).

On August 1, 2013, five weeks after the preemption advisory opinion in *Glynn*, Merck moved for the district court to issue an order to show cause why all cases in the MDL alleging injuries before September 14, 2010, should not be dismissed as preempted. MDL Dkt. 2857-1. Respondents objected to this procedure. JA50-56. The court entered the order to show cause as Merck proposed, giving respondents 45 days to respond. JA86-88.

Respondents opposed preemption. Respondents also argued that it would be procedurally improper to dismiss their claims on preemption grounds through the show-cause procedure. MDL Dkt. 2995-3.

The district court granted summary judgment to Merck and held that respondents' claims were preempted. Pet.App.113a-152a. The court concluded that, because of the *Glynn* advisory opinion, "the burden is therefore shifted to [respondents]" to defeat summary judgment. Pet.App.132a. It held that failure-to-warn claims based on the Warnings and Precautions section were preempted because the court had "already considered and rejected" respondents' arguments in *Glynn*. Pet.App.150a. The court rejected failure-to-warn claims based on the theory that Merck should have added a warning earlier to the

Adverse Reactions section, asserting that the theory was not adequately pleaded. Pet.App.147a-148a. The court also held that respondents' non-failure-to-warn claims were preempted because the court concluded — on the basis of a single allegation in a single complaint — that all of respondents' non-failure-to-warn claims were "merely disguised failure to warn causes of action." Pet.App.142a.

3. The Third Circuit vacated the district court's grant of summary judgment to Merck. Pet.App.4a. The court framed the question as whether the evidence that "FDA would have approved a properly-worded warning about the risk of thigh fractures" was sufficient for respondents to survive summary judgment. Pet.App.5a.

The Third Circuit concluded Merck was not entitled to summary judgment. The court held the record reasonably supported respondents' view that FDA rejected Merck's proposed warning "based on Merck's misleading use of the term 'stress fractures' rather than any fundamental disagreement with the underlying science" and that "FDA would not have rejected [a] proposed warning" of atypical femoral fractures. Pet.App.63a. The Third Circuit noted that "Merck repeatedly characterized the fractures at issue as 'stress fractures,'" Pet.App.65a, and that "[s]tress fractures are usually incomplete fractures that heal with rest, while atypical femoral fractures often are complete fractures that require surgical intervention," Pet.App.66a.

The Third Circuit read the Complete Response Letter as supporting respondents' position. That Letter criticized Merck's proposed "'[i]dentification of "stress fractures"'" and "'[d]iscussion of the risk factors for stress fractures,'" and "FDA did not give

any other reason for rejecting Merck's proposed warning." *Id.* (quoting JA511). The court reasoned that "[t]he combination of § 314.110's 'complete description' requirement" of all deficiencies in a complete response letter and "FDA's silence" in the Complete Response Letter concerning any lack of scientific evidence that Fosamax causes atypical femoral fractures "could certainly permit an inference about the FDA's contemporaneous thinking, and thereby an additional inference about how the FDA would have responded to a different warning." Pet.App.53a n.135.

The Third Circuit decided that, on remand, a jury, rather than a judge, should resolve the disputed factual questions presented by Merck's preemption defense. Pet.App.54a. The Third Circuit acknowledged "that courts are typically charged with determining the construction (*i.e.*, the legal effect) of a writing," such as the Complete Response Letter. Pet.App.52a. But that Letter did not resolve "whether the FDA would have approved a different label amendment than the one it actually rejected in the May 2009 letter." *Id.*

The court reasoned that, in this case, whether FDA would have rejected an adequate warning of atypical femoral fractures was a factual question within the traditional competence of juries because "an assessment of the probability of a future event should generally be categorized as a finding of fact," Pet.App.45a, which requires "weigh[ing] conflicting evidence and draw[ing] inferences from the facts — tasks that the Supreme Court tells us 'are jury functions, not those of a judge,'" Pet.App.47a (quoting *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986)). Merck stated at oral argument that its "single

best piece of evidence" in support of preemption was a memorandum written by Merck employee Charlotte Merritt ("Merritt memorandum") of a telephone call she had with Dr. Monroe of FDA in which he purportedly discussed the "conflicting nature of the literature" on atypical femoral fractures. Pet.App.49a n.125. Merck's reliance on the call notes confirmed for the Third Circuit the presence of disputed factual issues suitable for resolution by the jury: "at a minimum," a decisionmaker would need to make credibility determinations about Merck's employee, interpret the meaning and accuracy of the notes, infer the FDA official's intent, and then weigh those factors. *Id.*

The Third Circuit also interpreted *Levine* as imposing a "clear and convincing evidence" standard for a brand-name drug manufacturer's preemption defense, requiring the manufacturer to show that it was "highly probable that the FDA would not have approved a change to the drug's label." Pet.App.37a.[11]

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[11] The Third Circuit also held that Merck is not entitled to summary judgment on respondents' failure-to-warn claims involving the Adverse Reactions section of the Fosamax label or on respondents' non-failure-to-warn claims. Pet.App.69a-74a. Merck did not challenge those rulings in its certiorari petition and thus has forfeited any argument regarding the Third Circuit's decision to remand those claims. *See* Cert. Opp. 1; Sup. Ct. R. 14.1(a). Merck's half-sentence attempt (at 36) to revive a challenge to the non-failure-to-warn claims in its merits brief is improper and insufficient to properly present the issue in any event. *See, e.g., Anza v. Ideal Steel Supply Corp.*, 547 U.S. 451, 461 (2006) ("declin[ing] to address" argument that "has not been developed").

SUMMARY OF ARGUMENT

I.A. Failure-to-warn claims against brand-name drug manufacturers are not preempted absent clear evidence that FDA would have rescinded an adequate warning. The FDCA contains no applicable express preemption clause. Nor do failure-to-warn claims obstruct federal purposes. *See Levine*, 555 U.S. at 574.

B. Nothing in federal law makes it impossible for brand-name drug manufacturers to comply with a state-law duty inherent in a failure-to-warn claim by adding adequate warnings to an FDA-approved label. No provision of the FDCA prohibits such changes, and the CBE regulation expressly permits unilateral label changes to strengthen warnings. *See Levine*, 555 U.S. at 568; 21 C.F.R. § 314.70(c)(6)(iii)(A). Therefore, to establish impossibility preemption, the manufacturer must "show, by 'clear evidence,' that the FDA would have rescinded any change in the label and thereby demonstrate that it would in fact have been impossible to do under federal law what state law required." *Mensing*, 564 U.S. at 624 n.8 (quoting *Levine*, 555 U.S. at 571.

C. As *Levine* recognized, the FDAAA did not change the preemption analysis. When Congress authorized FDA to mandate label changes, it preserved manufacturers' ability to add such changes unilaterally and enacted a "[r]ule of construction" that FDA's new authority "shall not be construed to affect the responsibility of" the manufacturer "to maintain its label in accordance with existing requirements," including the CBE regulation. 21 U.S.C. § 355(*o*)(4)(I); *see Levine*, 555 U.S. at 571. FDA still relies on manufacturers to make most label changes. Thus, where FDA has not yet mandated a label change, one cannot infer that FDA would have rescinded a manufacturer's CBE supplement.

II. Merck failed to show, by clear evidence, that FDA would have rescinded an adequate warning of atypical femoral fractures.

A. The Complete Response Letter does not carry Merck's burden. Merck proposed to warn of minor "stress fractures," and its application did not accurately describe the atypical femoral fractures suffered by respondents. As the Complete Response Letter explained, FDA rejected Merck's proposal because of the inaccurate stress-fracture language. FDA also invited Merck to submit a revised warning that fixed this problem. JA511-12. That is consistent with the general function of complete response letters, which reject applications "in [their] present form," 73 Fed. Reg. at 39,589, while informing applicants of all deficiencies that must be remedied to obtain approval, *see* 21 C.F.R. § 314.110(a)(1). Merck's and the government's reading of the Complete Response Letter — as a final rejection of an atypical-femoral-fracture warning — cannot be squared with its text or the regulatory context. All the Complete Response Letter rejected was Merck's stress-fracture warning.

B. The informal FDA communications on which Merck relies also fail to prove impossibility. The Merritt memorandum, which Merck presented below as its "single best piece of evidence," Pet.App.49a n.125, raises factual questions regarding the accuracy of Merritt's notes and the meaning of the FDA official's reported remarks. FDA's earlier email stating it wanted to "work with" Merck on alternative warning language supports respondents because it contradicts Merck's position that FDA definitively rejected any label change. JA508.

C. FDA's actions in mandating an atypical-femoral-fracture warning in 2010 confirm that Merck

could have added a warning earlier. FDA was swayed to mandate the warning by the ASBMR Task Force report, which merely "summarized" existing "data," JA249, and "helped [FDA] understand these fractures a little bit better," JA494, by "clarify[ing] the features of atypical femur fractures," JA488. FDA presumably would have welcomed a similarly clarifying supplement from Merck, rather than its confusing stress-fracture label application.

III.A. Disputed factual questions regarding preemption should be presented to the jury. In civil actions at law, judges handle legal questions, while "predominantly factual issues are in most cases allocated to the jury." *City of Monterey v. Del Monte Dunes at Monterey, Ltd.*, 526 U.S. 687, 720 (1999). "[W]hether the facts establish the conditions for" a preemption defense "is a question for the jury." *Boyle v. United Techs. Corp.*, 487 U.S. 500, 514 (1988). Respondents agree with Merck and the government that the legal effect of the Complete Response Letter is a judge question. But that legal effect was limited to rejecting Merck's stress-fracture warning. Whether FDA would have rescinded a different warning presents the type of counterfactual question juries routinely decide.

B. The Third Circuit correctly applied a heightened standard of proof of impossibility. The FDCA and the CBE regulation make compliance with state law possible; to assert an impossibility-preemption defense based on speculation that FDA will take some future action to halt compliance with state law requires a persuasive showing. Nonetheless, it makes no difference to the outcome here whether this Court views "clear evidence" as imposing a "clear and convincing evidence" standard of proof or, as

the government contends (at 26), an "*interpretive* presumption against preemption."

C. In all events, the district court's judgment cannot stand because the court dismissed respondents' claims through a cursory show-cause procedure following an advisory opinion issued in another action to which respondents were not parties. Although the Third Circuit's disposition made it unnecessary to reach respondents' objections to the show-cause procedure, the district court's judgment could not be upheld without addressing those objections.

ARGUMENT

I. FAILURE-TO-WARN CLAIMS AGAINST BRAND-NAME DRUG MANUFACTURERS ARE NOT PREEMPTED UNLESS THE MANUFACTURER SHOWS BY CLEAR EVIDENCE THAT FDA WOULD HAVE RESCINDED AN ADEQUATE LABEL CHANGE

Federal law generally does not preempt failure-to-warn claims against brand-name drug manufacturers. No statute or regulation expressly preempts such claims, and failure-to-warn claims do not conflict with any aspect of the federal regulatory scheme. FDA regulations expressly permit (and in fact require) brand-name drug manufacturers to add warnings to FDA-approved labels to keep pace with scientific evidence of the drug's risks and to comply with state law.

A. The FDCA Does Not Expressly Preempt Failure-To-Warn Claims Against Brand-Name Drug Manufacturers, And Such Claims Pose No Obstacle To The Statute's Purposes

"Pre-emption of state law . . . occurs through the 'direct operation of the Supremacy Clause.'" *Kurns*

v. Railroad Friction Prods. Corp., 565 U.S. 625, 630 (2012) (quoting *Brown v. Hotel & Rest. Emps.*, 468 U.S. 491, 501 (1984)). "'[T]he purpose of Congress is the ultimate touchstone in every pre-emption case.'" *Levine*, 555 U.S. at 565 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)).

1. When Congress enacts a statute within its constitutional authority containing an express pre-emption clause, state law is preempted to the extent covered by that provision. *See, e.g., Gobeille v. Liberty Mut. Ins. Co.*, 136 S. Ct. 936, 943 (2016). Congress never has enacted an express preemption provision applicable to prescription drugs in the FDCA's 80-year history. Although Congress enacted a preemption provision for medical devices in 1976, it did not do the same for prescription drugs. *See Levine*, 555 U.S. at 574.

2. Failure-to-warn claims against brand-name drug manufacturers pose no "obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). This Court so held in *Levine*. There, FDA had appended a preamble to a drug-labeling regulation, which "declared that the FDCA establishes 'both a "floor" and a "ceiling,"' so that 'FDA approval of labeling . . . preempts conflicting or contrary State law.'" 555 U.S. at 575 (quoting 71 Fed. Reg. 3922, 3934-35 (Jan. 24, 2006)) (alteration in original). The Court rejected the preamble and Wyeth's reliance on it, concluding that "all evidence of Congress' purposes [wa]s . . . contrary" to the floor-and-ceiling argument. *Id.* at 574. The fact that Congress, while aware of prevalent state drug litigation, neither enacted a preemption clause nor a federal right of action was "powerful evidence that Congress did not intend FDA

oversight to be the exclusive means of ensuring drug safety and effectiveness." *Id.* at 575.[12]

B. A Brand-Name Drug Manufacturer Has The Power To Strengthen A Drug Label To Comply With State Law

State law is preempted "where it is 'impossible for a private party to comply with both state and federal requirements.'" *Mensing*, 564 U.S. at 618 (quoting *Freightliner Corp. v. Myrick*, 514 U.S. 280, 287 (1995)). "The question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it." *Id.* at 620.[13]

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[12] Justice Thomas concluded he could "no longer assent" to purposes-and-objectives preemption because it "giv[es] improperly broad pre-emptive effect to judicially manufactured policies, rather than to the statutory text enacted by Congress pursuant to the Constitution and the agency actions authorized thereby." *Levine*, 555 U.S. at 604 (Thomas, J., concurring in the judgment). In any event, purposes-and-objectives preemption does not apply to failure-to-warn claims against brand-name drug manufacturers because Congress consistently has preserved state law and manufacturers' authority to update their labels. *See id.* at 566-68 (majority).

This Court also has found preemption where federal law occupies an entire field. *See, e.g., Hughes v. Talen Energy Mktg., LLC*, 136 S. Ct. 1288, 1297 (2016). Merck never has argued for field preemption here, nor could it. *See Levine*, 555 U.S. at 567 (Congress has "t[a]k[en] care to preserve state law").

[13] A preemptive "direct conflict" also may occur "if federal law gives an individual the right to engage in certain behavior that state law prohibits." *Levine*, 555 U.S. at 590 (Thomas, J., concurring in the judgment). Such a conflict does not exist here because federal law "do[es] not give drug manufacturers an unconditional right to market their federally approved drug at all times with the precise label initially approved by the FDA." *Id.* at 592. Merck does not contend otherwise.

For failure-to-warn claims against brand-name drug manufacturers, the answer is yes: federal law permits manufacturers to strengthen label warnings to comply with state law. Nothing in the FDCA *prohibits* a brand-name manufacturer from changing an approved label. And the CBE regulation specifically authorizes a manufacturer to "chang[e] a label to 'add or strengthen a contraindication, warning, precaution, or adverse reaction'" and to do so "upon filing its supplemental application with the FDA; it need not wait for FDA approval." *Levine*, 555 U.S. at 568 (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)). Thus, when a brand-name manufacturer becomes aware of new information about patients suffering adverse events (or even new analysis of existing data), federal law permits that manufacturer to revise its label accordingly. *See id.* at 569.

In *Levine*, the Court allowed one narrow exception to the general rule that failure-to-warn claims against brand-name drug manufacturers are not preempted. As the Court explained, "FDA retains authority to reject labeling changes made pursuant to the CBE regulation in its review of the manufacturer's supplemental application." *Id.* at 571. The Court reasoned: "But absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements." *Id.*

In *Mensing*, the Court clarified the nature of the "clear evidence" exception: "the [*Levine*] Court noted that Wyeth could have attempted to show, by 'clear evidence,' that the FDA would have rescinded any change in the label and thereby demonstrate that it would in fact have been impossible to do under federal law what state law required." 564 U.S. at 624 n.8.

Merck acknowledged below that its preemption defense required showing "there is 'clear evidence' that the FDA would have rejected the addition of the warning that a plaintiff claims was necessary." Pet'r C.A. Br. 31.[14]

C. The 2007 FDCA Amendments Do Not Preempt State Law

The FDAAA did not change *Levine*'s impossibility-preemption analysis. Those amendments gave FDA authority, for the first time, to initiate a process to require manufacturers of approved drugs to change their labels. 21 U.S.C. § 355(*o*)(4). Congress did not add an express preemption clause, nor did it restrict manufacturers' ability to add changes unilaterally through CBE supplements. Rather, Congress enacted a "[r]ule of construction" that FDA's new authority "shall not be construed to affect the responsibility of" the manufacturer "to maintain its label in accordance with existing requirements," including the CBE regulation. *Id.* § 355(*o*)(4)(I). Thus, as the *Levine* Court recognized, the FDAAA "reaffirmed the manufacturer's obligations and referred specifically to the CBE regulation, which both reflects the manufacturer's ultimate responsibility for its label and provides a mechanism for adding safety information to the label prior to FDA approval." 555 U.S. at 571.[15]

Merck (at 22, 31-32) and PhRMA (at 4-5) err in arguing that one can infer impossibility where FDA has not (yet) exercised its authority to mandate

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[14] Accordingly, Merck has waived any argument that a lesser showing is required. *See* Supp. Cert. Opp. 4.

[15] Thus, *Levine* itself rejected PhRMA's argument (at 4) that the FDAAA "modif[ies] the preemption equation presented in *Levine*."

a label change. In Merck's view (at 22, 39), FDA has a "statutory obligation" to mandate a label change whenever such a change is scientifically justified, and it would therefore constitute "agency lawlessness" for FDA to rely on a manufacturer to update a label, rather than to mandate a change itself.

Merck's argument is at odds with the statutory text, as well as FDA guidance and practice. The FDAAA confers upon FDA *discretionary* authority to mandate label changes, while "reaffirm[ing] the manufacturer's obligations" to keep its label up to date. *Levine*, 555 U.S. at 571. The statute provides: "If the Secretary [of Health and Human Services] becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug, the Secretary shall" initiate a process to mandate a label change. 21 U.S.C. § 355(*o*)(4)(A). The Court long has understood this familiar structure — that an executive official *shall* act *if* the official determines that action is warranted — as conferring discretionary authority to determine when to act. For example, in *United States v. George S. Bush & Co.*, 310 U.S. 371 (1940), the Court considered a statute providing that "the President 'shall by proclamation approve [tariff rates] . . . , if in his judgment such rates . . . are . . . necessary to equalize . . . differences in costs of production.'" *Id.* at 376-77. The Court concluded that this statute conferred "discretionary power" on the President, which was "not subject to review." *Id.* at 380.

FDA has issued guidance confirming it regards the authority to mandate label changes as discretionary: "FDA does not anticipate that all labeling changes that may be related to safety will be required and reviewed under [§ 355(*o*)(4)]. For other labeling changes, application holders may continue to submit

labeling supplements using standard procedures," including the CBE regulation.[16]

FDA practice confirms that, following the FDAAA's enactment, the agency has continued to rely on manufacturers to make most label updates, exercising its power to mandate changes only on rare occasions. In the two years following the FDAAA's enactment (through September 14, 2009), FDA required safety-related labeling changes 22 times.[17] During the partially overlapping two-year period of 2009 and 2010, drug manufacturers submitted 363 CBE supplements for the same type of change.[18] Thus, far more label updates resulted from unilateral manufacturer action than FDA mandate.

The reason FDA primarily has relied on manufacturers to make label changes is obvious: "FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the post-marketing phase as new risks emerge." *Levine*, 555 U.S. at 578-79 (footnote omitted). As Sen. Kennedy explained in his statement regarding the FDAAA's enactment, Merck's annual sales of Fosamax Plus D

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[16] FDA, *Guidance for Industry Safety: Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* 5-6 (July 2013), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf.

[17] *See* FDA, FDA Implementation – Highlights Two Years After Enactment, https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm184271.htm.

[18] *See* FDA, *Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products* 7, https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/economicanalyses/ucm375128.pdf.

"alone exceed the entire $120 million FDA budget for drug safety," even after that budget was more than doubled by the FDAAA. 153 Cong. Rec. S11,831, S11,832 (daily ed. Sept. 20, 2007).

The FDAAA reaffirmed manufacturers' regulatory duty to keep their labels up to date. It does not insulate manufacturers from liability or authorize them to wait to act until mandated by FDA.[19]

II. MERCK HAS NOT SHOWN BY CLEAR EVIDENCE THAT FDA WOULD HAVE RESCINDED AN ADEQUATE WARNING OF ATYPICAL FEMORAL FRACTURES

Merck failed to show that it was impossible to comply with state law. Merck never attempted to add an adequate warning of atypical femoral fractures, and thus the question of how FDA would have responded to such a warning is hypothetical. When Merck proposed to add a warning that focused on "stress fractures," FDA issued a Complete Response Letter explaining it was rejecting Merck's proposal because of the unsupported discussion of the link between stress fractures and atypical femoral fractures. The additional informal FDA communications (and Merck's self-serving hearsay accounts of those communications) upon which Merck relies are equivocal (at best) and cannot establish preemption. The relevant history — FDA mandated an atypical-femoral-fracture warning soon after a report accurately

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[19] Congress considered and rejected such an approach. The Senate bill that became the FDAAA provided that a manufacturer could not strengthen a label until ordered to do so by FDA. *See* S. 1082, 110th Cong. § 208 (2007). But Congress rejected that provision and "[i]nstead . . . adopted a rule of construction to make it clear that manufacturers remain responsible for updating their labels." *Levine*, 555 U.S. at 567-68.

described the fractures, in contrast to Merck's inaccurate "stress fracture" characterization — confirms that Merck *could* have added an accurate atypical-femoral-fracture warning much earlier.

By claiming broad preemption based on a government *amicus* brief and informal agency communications, Merck stretches impossibility preemption beyond the breaking point, advancing a defense that more closely resembles the type of obstacle preemption based on "agency musings" rejected in *Levine*, 555 U.S. at 573-80; *id.* at 587 (Thomas, J., concurring in the judgment).

A. The Complete Response Letter Regarding Merck's Proposed Stress-Fracture Warning Did Not Preclude Merck From Adding An Adequate Warning Of Atypical Femoral Fractures

According to Merck (at 1, 34-35), it proposed a warning "addressing th[e] risk" of "atypical femoral fractures," and, in FDA's Complete Response Letter, "FDA rejected Merck's request to warn about atypical femoral fractures," making it "impossible for Merck to revise its label to conform to the state-law duties that respondents allege."

Every aspect of Merck's factual framing is wrong. Merck never proposed a warning of atypical femoral fractures to FDA. In an attempt to minimize the risk, Merck proposed to warn of "stress fractures," which are widely understood as minor fractures far less serious than atypical femoral fractures. In the Complete Response Letter, FDA explained that it rejected Merck's proposal because Merck's identification and discussion of "stress fractures" did not match the literature on atypical femoral fractures. FDA told Merck it could submit a revised proposal remedying that deficiency. The plain import of the Complete

Response Letter, and its formal legal effect, was to reject Merck's proposed stress-fracture warning. Far from *precluding* Merck from adding an adequate warning of atypical femoral fractures, FDA *invited* Merck to do so.

1. Merck never proposed an accurate warning of atypical femoral fractures

Merck's proposed warning minimized and mischaracterized the risk by focusing on "stress fractures" of the femur, JA707, which are much less serious than the atypical femoral fractures suffered by respondents. The heading and first sentence of Merck's proposal referred to "[l]ow-energy" "femoral shaft" fractures, but did not describe the nature of the fractures adequately or specifically. *Id.* Every sentence after that described the fractures as "stress fractures." *See, e.g.*, *id.* (patients experienced pain "often associated with imaging features of stress fracture"; "stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonate"; "patients with suspected stress fractures should be evaluated including evaluation for known causes and risk factors (e.g., . . . previous stress fracture . . .)"; "[i]nterruption of bisphosphonate therapy in patients with stress fractures should be considered").

Merck's proposed language warned of femoral stress fractures. But a simple comparison of x-rays of an atypical femoral fracture and a femoral stress fracture illustrates the difference. *See supra* pp. 14-15. One looks like a pencil snapped in two. The other is a slight protrusion, barely perceptible to people without radiology training.

Both FDA and Merck have acknowledged the crucial distinction between stress fractures and atypical femoral fractures. In 2010, FDA explained that

characterizing atypical femoral fractures as "stress fractures" would "contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use" because, "for most practitioners, the term 'stress fracture' represents a minor fracture." JA566. In crafting a response, Merck acknowledged internally that "most of the stress fractures general physicians have seen are associated with repetitive stress injury related to exercise (e.g., running) in younger adults, and that this type of stress fracture generally heals well with rest." C.A.App.1573; *see also* JA145-46 (Burr Decl. ¶ 86) (atypical femoral fractures are "much more significant than 'garden-variety' stress fractures").

While in rare cases stress fractures can progress into atypical femoral fractures, Merck's proposed warning "improperly conflated the underlying fracture mechanism that leads to AFFs with the ultimate outcome." JA144 (Burr Decl. ¶ 84). As Merck itself acknowledged, the rare stress fractures that can develop into atypical femoral fractures differ from the ubiquitous stress fractures that result from overloading a heavy bone (e.g., through athletic activity). C.A.App.1341. Merck's proposed warning listed "risk factors" for stress fractures that "simply were not associated with AFF," JA142 (Burr Decl. ¶ 79), including "extreme or increased exercise," JA707.

Merck's application also contained a clinical overview that obscured the nature of atypical femoral fractures. JA745-61. The clinical overview failed to "provide the FDA with any possible pathogenesis for AFF from long-term Fosamax," meaning the scientific mechanism through which Fosamax causes atypical femoral fractures. JA136 (Burr Decl. ¶ 69). Merck's overview also erroneously described atypical femoral fractures as similar to fractures suffered by persons

who did not use Fosamax, obscuring that atypical femoral fractures were a rare form of fracture predominantly seen in bisphosphonate users. JA138 (*id.* ¶ 72) (quoting JA755). Merck's protestation (at 35) that it disclosed scientific evidence to FDA thus rings hollow; while Merck disclosed some of the relevant literature, its clinical overview tended to obscure rather than enlighten the meaning of that literature.

This case is similar to *Levine* in that the manufacturer sought preemption based on FDA's rejection of proposed warning language that did not actually address the risk that caused the plaintiff's injuries. In *Levine*, Wyeth and the dissent argued that Ms. Levine's failure-to-warn claims were preempted because Wyeth proposed warning language regarding the risk of intravenous injection of Phenergan, and "FDA rejected Wyeth's proposal." 555 U.S. at 605 n.1 (Alito, J., dissenting). Although Wyeth's proposal addressed intravenous injection generally, it did not warn adequately of the specific dangers of using the IV-push method. *Id.* at 572 & n.5 (majority). The majority therefore rejected Wyeth's and the dissent's argument because Wyeth had not "attempted to give the kind of warning required by the Vermont jury." *Id.* at 572. The same is true here. Merck's proposal described a different type of fracture from those suffered by respondents, and it was not "the kind of warning" that would satisfy Merck's state-law duty to warn.

2. The Complete Response Letter did not preclude Merck from adding an adequate warning of atypical femoral fractures through a CBE supplement

FDA rejected Merck's proposal because of the inaccurate discussion of stress fractures and then

invited Merck to submit alternative language. The Complete Response Letter offered only one reason for rejecting Merck's stress-fracture warning: Merck's identification of the risk as, and discussion of, "stress fractures." FDA's explanation is important because a complete response letter is required to "describe all of the specific deficiencies that the agency has identified in an application." 21 C.F.R. § 314.110(a)(1).

The first sentence of FDA's explanation for rejecting the stress-fracture warning (quoted in full *supra* p. 16) states that Merck's "justification" for its "proposed . . . language is inadequate." JA511. FDA limited its criticism to Merck's "proposed . . . language" regarding stress fractures, not to warnings of atypical femoral fractures. The next sentence explains that the justification for Merck's language was inadequate because "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." *Id.* FDA's critique was not that the "literature" contained insufficient evidence that Fosamax causes atypical femoral fractures; it was that Merck's discussion of "stress fractures" misidentified the nature of the risk shown by the literature. Next, FDA explained that "[d]iscussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and postmarketing adverse event reporting." JA511-12. Again, FDA did not note any lack of support in the "available literature" or "postmarketing adverse event reporting" for the notion that Fosamax causes atypical femoral fractures. Rather, what was "not adequately supported" was "[d]iscussion of the risk factors for stress fractures." A warning listing risk factors unrelated to atypical femoral fractures would confuse physicians and patients and make it less likely

they would recognize the risk connecting Fosamax use with an atypical femoral fracture.[20]

Merck's assertion (at 34) that FDA issued a "flat . . . rejection" of any femur-fracture warning also cannot be squared with FDA's invitation to resubmit the application. FDA stated that "we cannot approve these applications *in their present form*." JA511 (emphasis added). It invited Merck "to resubmit" its application after "fully address[ing] all the deficiencies listed," JA512; *see* 73 Fed. Reg. at 39,589 (complete response letters "convey that [FDA] cannot approve an application *in its present form*," while "informing sponsors *of changes that must be made before* an application can be approved, with *no implication* as to the ultimate approvability of the application") (emphases added).[21] Signifying that the process was ongoing, FDA invited Merck to call an FDA regulatory project manager with any questions. JA513. FDA's approach was fully consistent with "the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times." *Levine*, 555 U.S. at 579. In no conceivable understanding of the English language was it "impossible" for Merck to add appropriate warning language.

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[20] *See* JA142 (Burr Decl. ¶ 79) ("When the Task Force examined the actual data, many of the 'risk factors' identified by Merck in its submission to the FDA simply were not associated with AFF.").

[21] In practice, FDA regularly approves resubmitted applications after deficiencies identified in a complete response letter are remedied. *See generally* Theresa Allio, FDAnews, *FDA Complete Response Letter Analysis: How 51 Companies Turned Failure into Success* (2013) (identifying 51 drugs approved from 2009 through 2013 following complete response letters). For 47% of those applications discussed in that study, the manufacturer secured approval after remedying a labeling deficiency identified in the complete response letter. *Id.* at 11-12.

3. The government's *post hoc* interpretations of the Complete Response Letter are implausible and inconsistent with FDA regulations

a. The Complete Response Letter contains not a hint of what Merck (at 49) and the government (at 30-31) now contend was the real reason behind FDA's decision: the supposed lack of scientific evidence that Fosamax causes atypical femoral fractures. Try as they might, neither the government nor Merck can identify any language in the Complete Response Letter citing insufficient evidence of a causal connection between Fosamax and atypical femoral fractures. Instead, FDA cited inadequate scientific support for "[i]dentification of 'stress fractures'" and "[d]iscussion of the risk factors for stress fractures." JA511-12.

Merck's contemporaneous understanding of the Complete Response Letter contradicts its *post hoc* litigation position. The day Merck received the Complete Response Letter, Merck's U.S. Regulatory Liaison James Adams informed his colleagues that FDA "believes that 'stress fractures' may not be clearly related to atypical subtrochanteric fractures." JA515. Merck's Director of Clinical Research Arthur Santora responded that "FDA wouldn't let us mention stress fractures." JA517. Merck's scientists correctly interpreted FDA's Complete Response Letter; its lawyers have not.

The government argues (at 30-31) that FDA's approval of Adverse Reactions language roughly matching the heading of Merck's proposed Warnings and Precautions language means that FDA intended to reject any Warnings and Precautions language addressing atypical femoral fractures. On the contrary, FDA's action shows it was willing to approve a

warning of low-energy femoral fractures but unwilling to approve language that misidentified atypical femoral fractures as stress fractures. FDA's approval of the Adverse Reactions language in May 2009 thus strongly supports the conclusion that it was possible for Merck to warn of atypical femoral fractures in the Warnings and Precautions section as well, so long as it properly identified and described the risk at issue.

b. Two FDA regulations relied on by Merck (at 32) and the government (at 6, 32) do not support their interpretation of the Complete Response Letter.

First, an FDA regulation provides that, "if the only deficiencies" in an application "concern editorial or similar minor deficiencies in the draft labeling," FDA will approve the application contingent upon specified labeling changes. 21 C.F.R. § 314.105(b). But the deficiencies in Merck's proposed warning were neither editorial nor minor. Merck wholly misdescribed the risk and listed scientifically unsupported risk factors. *See supra* Part II.A.1. Given the magnitude of the deficiencies, FDA reasonably relied on Merck to remedy them in the first instance.

Second, another regulation states that "FDA reviewers shall make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application." 21 C.F.R. § 314.102(b). FDA did so by communicating the deficiencies to Merck in its Complete Response Letter. JA511-12. Moreover, Merck's deficiencies were not easily correctable but rather would have required Merck to rewrite its proposal to address atypical femoral fractures, rather than stress fractures.

The regulation directly on point, governing complete response letters, further undermines Merck's position. Under that regulation, FDA was required to "describe

all of the specific deficiencies" in Merck's application. 21 C.F.R. § 314.110(a)(1) (emphasis added). The letter here did not describe the supposed lack of evidence connecting Fosamax to atypical femoral fractures. Merck's preemption theory thus depends on the premise that FDA submitted a non-compliant Complete Response Letter listing a false reason for denying the application and omitting discussion of the true reason. *See* Pet.App.53a n.135 (Merck's argument depends on supposition that FDA did not "follow[] § 314.110 to a T"). The far more natural inference is that FDA meant what it said: it rejected Merck's proposal because of the unsupported stress-fracture warning.[22]

c. Merck (at 37-38) and the government (at 33) err in analogizing this case to *Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803 (7th Cir. 2018), in which the Seventh Circuit found that claims were preempted based on detailed FDA scientific analysis rejecting a warning. There, GlaxoSmithKline added the type of warning the plaintiff contended was required (suicide risk in older adults) through a CBE supplement, but FDA ordered GlaxoSmithKline to remove the warning

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[22] The government's attempt (at 32) to minimize the complete-description requirement fails. As the government notes (*id.*), one exception exists to this requirement: "If FDA determines, after an application is filed . . . , that the data submitted are inadequate to support approval, the agency might issue a complete response letter without first conducting required inspections and/or reviewing proposed product labeling." 21 C.F.R. § 314.110(a)(3). That provision refers to an NDA, not a labeling supplement. In an NDA, where data submitted are inadequate to support approval of the drug (e.g., for failure to demonstrate safety or efficacy), it makes perfect sense for FDA not to inspect manufacturing facilities or review labeling. For an application that solely seeks to amend labeling, however, FDA cannot evaluate adequacy of the "data submitted" without "reviewing proposed product labeling."

based on its "meta-analysis," which "considered 372 placebo-controlled clinical trials and involved nearly 100,000 adult patients," and "concluded that the 'net effect appears to be neutral on suicidal behavior but possibly protective for suicidality for adults between the ages of 25 and 64.'" *Id.* at 809; *see Dolin v. SmithKline Beecham Corp.*, No. 1:12-cv-06403, Dkt. 589-14 (N.D. Ill. Sept. 25, 2017) (64-page meta-analysis).[23]

Likewise, in *Cerveny v. Aventis, Inc.*, 855 F.3d 1091 (10th Cir. 2017), the Tenth Circuit found preemption where FDA rejected the warning sought by the plaintiffs in a letter that meticulously analyzed the evidence and picked apart the scientific arguments. *Id.* at 1101; *see* Appellant App. 383-94, *Cerveny v. Aventis, Inc.*, No. 16-4050 (10th Cir. July 11, 2016) (FDA letter). As illustrated by *Dolin* and *Cerveny*, if FDA had concluded in May 2009 that insufficient evidence linked Fosamax to atypical femoral fractures, it would have said so and explained its conclusion in the Complete Response Letter.

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[23] The chronology of FDA's actions in *Dolin* supports respondents' position. There, FDA allowed GlaxoSmithKline to maintain its CBE-added warning for more than a year, before FDA finished studying the issue and directed uniform warnings for the class of drugs, SSRIs, that excluded GlaxoSmithKline's language. *Dolin*, 901 F.3d at 808-09. Here, FDA was actively studying the relationship between bisphosphonates and atypical femoral fractures since no later than June 2008. JA280. FDA's actions in *Dolin* strongly suggest that, had Merck added an atypical-femoral-fracture warning through a CBE supplement while FDA was studying the issue, FDA would not have rescinded it. Rather, FDA would have allowed Merck to maintain the warning until FDA completed its study and decided to mandate that all bisphosphonate manufacturers add atypical-femoral-fracture warnings.

d. In asserting (at 50) that the government's certiorari-stage brief makes this case a "slam dunk," Merck misunderstands that brief. The government's *amicus* briefs in this case are not (as Merck contends at 49-50) a factual representation from FDA that FDA would not have approved a femur-fracture warning before October 2010. Rather, the briefs convey the government's legal argument (which is incorrect for the reasons explained).

In both briefs, the government made clear when it was making specific factual representations regarding FDA's actions.[24] By contrast, the government described its interpretation of the Complete Response Letter as its "conclusion," purportedly based on its reading of the Letter and other regulatory context. U.S. Cert. Br. 19. The merits-stage brief confirmed (at 32) that interpretation to be its "understanding."

Nor is the government's brief entitled to deference. When an agency has enacted a regulation, this Court has given "some weight" to the agency's explanation of the regulation's objectives in determining whether state law obstructs a significant federal objective. *See Geier v. American Honda Motor Co.*, 529 U.S. 861, 883 (2000). But, here, no regulation purportedly preempts state law. *See Levine*, 555 U.S. at 582 (Breyer, J., concurring) (rejecting U.S. brief arguing for preemption in absence of "lawful specific regulations" with preemptive effect); *see also Mensing*, 564 U.S. at 613 n.3 ("[W]e do not defer to an agency's ultimate conclusion about whether state law should be pre-empted.").

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[24] *See* U.S. Cert. Br. 3 n.2 ("FDA has informed this Office [of the Solicitor General]"); *id.* at 5 ("FDA . . . confirmed to this Office"); *id.* at 7 n.6; *accord* U.S. Br. 3 n.2, 5, 7 n.6.

More recently, several Justices have expressed profound skepticism of judicial deference to government litigation briefs setting forth new legal interpretations. *See E.I. Du Pont de Nemours & Co. v. Smiley*, 138 S. Ct. 2563, 2564 (2018) (Gorsuch, J., joined by Roberts, C.J., and Thomas, J., respecting denial of certiorari) (expressing concern that deference to agency litigation briefs may raise "serious equal protection concerns" and could undermine the Administrative Procedure Act "by incentivizing agencies to regulate by *amicus* brief"); *Mutual Pharm. Co. v. Bartlett*, 133 S. Ct. 2466, 2481 (2013) (Breyer, J., joined by Kagan, J., dissenting) (refusing to defer to agency views "set forth . . . only in briefs filed in litigation, not in regulations, interpretations, or similar agency work product").

Even if the Court accorded minimal consideration to the government's brief under *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944), that would make no difference. Under *Skidmore*, the weight of an agency interpretation hinges upon "the thoroughness evident in its consideration, the validity of its reasoning, its consistency with earlier and later pronouncements, and all those factors which give it power to persuade." *Id.* at 140. Here, the government's brief glossed over the difference between stress fractures and atypical femoral fractures, misinterpreted the plain language of the Complete Response Letter, and ignored FDA regulations, guidance, and practice that cut against the government's litigation position. The Court should reject the government's view, just as it did in *Levine*.

B. Merck's Informal Communications With FDA Do Not Establish Preemption

In its merits brief, Merck dramatically shifted course from its Third Circuit arguments. Here, Merck

argues primarily (at 21-23, 31-40) that the Complete Response Letter preempts respondents' claims. Below, Merck "direct[ed] [the Third Circuit's] attention away from [the Complete Response Letter] and instead toward a series of informal FDA communications from the same time period between Dr. Monroe [of FDA] and Merck." Pet.App.47a. Perhaps recognizing the weakness of its current theory, Merck still relies on these informal communications (at i, 12-13, 34-35) as a fallback. Merck's old theory fares no better than its new one. Its discussion of the informal communications is nothing more than speculation that FDA *might* have rejected an adequate warning. That falls far short of the clear evidence of impossibility this Court's precedents require.

The Merritt memorandum, which Merck touted below as its "single best piece of evidence," Pet.App.49a n.125, does not support preemption.[25] That document purports to summarize a phone call that a Merck employee had with Dr. Monroe, the FDA official who wrote the Complete Response Letter. JA764-67. The memorandum, which refers to "[t]he conflicting nature of the literature," JA767, at best raises factual questions regarding the accuracy of Merritt's notes and the content and meaning of what Dr. Monroe said. If "agency musings" are insufficient to preempt state law, *Levine*, 555 U.S. at 587 (Thomas, J., concurring in the judgment), then surely a regulated party's self-serving hearsay account of such musings cannot suffice.

Merck also relies (at 12-13, 35) on an April 2009 email from FDA to Merck stating that an Adverse Reactions label change could be approved immediately,

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[25] Merck continues to rely on this document. Pet. Br. i, 12, 34.

"[i]f Merck agrees to hold off on the W&P [Warnings and Precautions] language at this time," and that FDA "would then work with . . . Merck to decide on language for a W&P atypical fracture language, if it is warranted." JA508. That document supports respondents. FDA's willingness to "work with" Merck on alternative "W&P atypical fracture language" contradicts Merck's reading of the Complete Response Letter as a definitive rejection of any femur-fracture warning. The Third Circuit correctly concluded that the record supported the inference that "it was Merck's failure to re-submit a revised CBE or PAS without stress-fracture language, rather than the FDA's supposedly intransigent stance on the science, that prevented the FDA from approving a label change." Pet.App.67a.

C. FDA's Decision To Mandate An Atypical-Femoral-Fracture Warning Undercuts Merck's Preemption Defense

FDA's decision to *require* bisphosphonate manufacturers to add an atypical-femoral-fracture warning — expressed in a series of announcements in 2010 — confirms that it was possible for Merck to add an adequate warning.

In March 2010, spurred by "news reports" connecting bisphosphonates to atypical femoral fractures, FDA announced it was working "with outside experts," including the ASBMR Task Force, "to gather additional information." JA519-20.[26] On September

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[26] Merck notes (at 34) FDA stated the data "have not shown a *clear* connection" between bisphosphonates and atypical femoral fractures. JA519 (emphasis added). That statement does not support impossibility preemption because the federal standard for adding a warning is far lower: Merck was permitted (and obligated) to add a warning "as soon as there is reasonable evidence

14, 2010, after the Task Force published its report, FDA announced that the Task Force's "case definition that describes the atypical features of these unusual fractures" would "help greatly" in understanding the issue. JA523. On October 13, 2010, when FDA directed bisphosphonate manufacturers to discuss atypical femoral fractures in the Warnings and Precautions section, FDA explained the Task Force report "summarized" "data ... regarding bisphosphonates and atypical subtrochanteric and diaphyseal femur fractures." JA249. In a conference call that same day, an FDA official explained the report "helped us understand these fractures a little bit better," JA494, and "helped to clarify the features of atypical femur fractures," JA488.[27]

Thus, FDA did not view the Task Force report as a sea change in the data connecting bisphosphonates to atypical femoral fractures. Instead, the report "summarized" existing data in a way that "clarif[ied] the features of atypical femur fractures," JA249, 488, and that clarification spurred FDA to mandate a warning. Far from showing that FDA would have rejected an atypical-femoral-fracture warning before the report, as Merck (at 34-35) and the government (at 33-34) assert, the context indicates that Merck would have succeeded had it submitted an application that accurately described and warned of atypical femoral

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of a c[illegible]al association with a drug; a causal relationship need not have been definitely established." 21 C.F.R. § 201.57(c)(6)(i). Indeed, even when FDA mandated a warning in October 2010, the agency noted it was "not *clear* if bisphosphonates are the cause" of atypical femoral fractures. JA247 (emphasis added).

[27] Dr. Burr, a principal author of the report, confirmed the report presented no new data but merely reviewed and reported on "the currently available information" regarding atypical femoral fractures. JA133-34 (¶ 62).

fractures, rather than conflating them with stress fractures. After all, the Task Force report did little more than clear up the confusion caused by Merck's own stress-fracture proposal.

Finally, Merck's acquiescence to FDA's demand to add a warning removes any doubt about the current state of the science. JA223-24. Merck, respondents, and FDA all agree there is reasonable evidence Fosamax causes atypical femoral fractures. This is not a case where a successful lawsuit could force a manufacturer to over-warn beyond the balance preferred by FDA. *Cf.* PhRMA Br. 22-25 (reiterating rejected concern that tort suits could upset "balance" in drug labeling); *Levine*, 555 U.S. at 579 ("State tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly.").

III. THE THIRD CIRCUIT'S GUIDANCE FOR THE DISTRICT COURT ON REMAND WAS CORRECT

In denying summary judgment, the Third Circuit gave guidance to the district court on questions regarding the allocation of fact-finding between the judge and jury, as well as the standard of proof. According to Merck (at 42), the Third Circuit's conclusion that the jury should resolve disputed factual questions has no bearing on whether the Third Circuit's denial of summary judgment should be affirmed, because "the identity of the ultimate factfinder" is distinct from the question "whether any genuine dispute of material fact existed."[28] Merck also describes

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[28] In its invitation brief, the government opined that "the question is close" whether certiorari was warranted, but narrowly recommended certiorari because the "underlying issue" of whether preemption issues should be submitted to "courts" or

(at 40) the Third Circuit's discussion of the standard of proof as "irrelevant" to whether the denial of summary judgment should be affirmed. Respondents agree. This Court may affirm the Third Circuit's denial of summary judgment without reaching those issues. If the Court does reach them, the Third Circuit's approaches are correct.

A. A Jury Should Resolve Disputed Factual Questions Necessary For Preemption

The question whether FDA would have rescinded an adequate atypical-femoral-fracture warning that Merck never proposed is factual, and the Court should adhere to the traditional rule that juries decide factual questions in common-law tort suits.

1. In civil actions at law, judges handle legal questions, while "predominantly factual issues are in most cases allocated to the jury." *Monterey*, 526 U.S. at 720. That allocation "rests on a firm historical foundation," which ultimately derives from the Seventh Amendment. *Id.* at 718, 720. Questions that involve both "legal aspect[s]" and "factual component[s]" are "mixed question[s] of fact and law." *Id.* at 721. It is "proper to submit" the "fact-bound" aspects of such questions to the jury. *Id.*; *see also id.* at 732 (Scalia, J., concurring in part and concurring in the judgment) (separating mixed question into "two subquestions": "a question of law for the court" and "a question of fact for the jury").

That analysis applies equally to factual issues relevant to preemption. In *Boyle*, the Court held that "whether the facts establish the conditions for"

"juries" was "significant." U.S. Cert. Br. 22. Now that Merck has stated (at 40, 42) that the issue is "moot[]" and "there was no need" for the Third Circuit to address it, the basis on which the Court granted certiorari no longer exists.

the government-contractor-preemption defense "is a question for the jury," unless the summary-judgment standard is satisfied. 487 U.S. at 514. The government unpersuasively attempts (at 28-29) to distinguish *Boyle* as involving "factbound showings," unlike this preemption defense. But, under *Boyle*, a jury determines whether government officials had knowledge of dangers of equipment when approving a contract. 487 U.S. at 514. That determination is no more factbound than determining whether FDA officials clearly evinced an intent to reject a hypothetical warning the drug manufacturer never proposed.

Juries routinely determine outcomes in a counterfactual world, such as whether a drug manufacturer has shown, by clear evidence, that FDA would have rejected an adequate warning. In most tort cases, the jury decides causation and damages by comparing a plaintiff's current position to the plaintiff's hypothetical position but for the defendant's tortious actions. *See* Restatement (Third) of Torts: Liability for Physical and Emotional Harm § 26 (2010) ("Conduct is a factual cause of harm when the harm would not have occurred absent the conduct."); Restatement (Second) of Torts § 906 cmt. c (1979) (damages include "loss of prospective earnings based upon the evidence concerning what [plaintiff] probably could have earned but for the harm"). Predicting FDA's response to a hypothetical CBE supplement adding an adequate warning is likewise a counterfactual analysis appropriate for resolution by the jury.

The fact that this preemption question involves assessing actions of government officials for purposes of deciding a constitutional defense does not change that conclusion. This Court and other courts regularly submit such questions to the jury. For example, in

Monterey, the takings claim required assessing whether "the city's decision . . . bore a reasonable relationship to its proffered justifications," which the Court held was properly submitted to the jury. 526 U.S. at 721. Likewise, in First Amendment employment-retaliation cases, juries plumb the motivations of government officials to "find whether the [employee's] discharge was caused by" protected speech. *Id.* at 731 (Scalia, J., concurring in part and concurring in the judgment) (citing *Horstkoetter v. Department of Pub. Safety*, 159 F.3d 1265, 1271 (10th Cir. 1998)). In Fourth Amendment excessive-force cases, the reasonableness of an officer's actions is generally assessed by a jury, unless the evidence is so one-sided that a reasonable jury could reach only one conclusion. *See Scott v. Harris*, 550 U.S. 372, 380-81 & n.8 (2007).

Merck and the government offer no persuasive justification for treating the *Levine* "clear evidence" inquiry any different from other factual questions. The government (at 20-21) and Merck (at 44-45) argue that, even if the preemption issue involves factual questions, the court should be the factfinder. They attempt to analogize to *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 388-91 (1996), which held that construction of written patent claims is for the court, even if it involves some factual elements. That analogy fails because the question in *Markman* was construction of a written legal document, which traditionally has been allocated to judges. By contrast, the question under the "clear evidence" exception is whether the manufacturer has supported its prediction about FDA's response to a hypothetical CBE supplement with clear evidence, which is the sort

of factual question that courts traditionally submit to juries.

Finally, the specific context of federal drug regulation provides no justification for shielding factual questions from juries. The FDCA assigns to juries the task of assessing the adequacy and accuracy of drug labels in determining whether drugs are misbranded. 21 U.S.C. § 352(a), (f); *see Levine*, 555 U.S. at 570 ("the statute contemplates that federal juries will resolve most misbranding claims"). Neither Merck nor the government articulates any principled reason why juries are competent to handle misbranding claims but not factual questions related to preemption.

2. To be sure, it frequently will be possible for courts to resolve preemption defenses on summary judgment, either for or against preemption, based on an undisputed regulatory record. And the legal effect of a written regulatory action, such as the Complete Response Letter, is a question for the court. Resp. Supp. C.A. Br. 4. But Merck and the government err in contending that the answer to that question justifies preemption here. The Complete Response Letter in this case rejected a stress-fracture warning, not an atypical-femoral-fracture warning. Thus, Merck's defense required showing that FDA would have rejected "a different label amendment than the one it actually rejected in the May 2009 letter." Pet.App.52a.

Respondents argued below, and still believe, that Merck's preemption defense fails as a matter of law because the text of the Complete Response Letter provides no support for Merck's contention that FDA had rejected *any* femur-fracture warning. Resp. Supp. C.A. Br. 4. Yet the Third Circuit concluded that jury resolution was required because "Merck . . . direct[ed]

[the Third Circuit's] attention away from [the Complete Response Letter] and instead toward a series of informal FDA communications" that purportedly revealed FDA's true intentions. Pet.App.47a; *see also* Pet'r C.A. Br. 40-48, 50-53 (relying on informal FDA statements). Merck relies (at 34-35) on those informal communications (including the Merritt memorandum[29]) not to interpret the Complete Response Letter, as the government suggests (at 27), but to furnish a basis for preemption not found in that Letter. Although Merck asserts (at 36-37) that the Third Circuit erred by treating the Complete Response Letter as "simply one piece of evidence for the jury to consider" along with informal FDA communications, Merck *invited* that approach.

The Third Circuit correctly recognized that Merck's preemption theory implicated "credibility determination[s]" of Merritt and required "weigh[ing] ... competing inferences" about Dr. Monroe's intent in light of supposed conflicts between FDA's official regulatory action and informal communications. Pet.App.49a n.125. Those "are precisely the types of personal evaluations and weight-of-the-evidence assessments that [courts] commit to jurors in the first instance." *Id.*

B. The Third Circuit Correctly Required A Heightened Standard Of Proof For Impossibility Preemption Under *Levine*

A manufacturer must satisfy a heightened standard of proof to qualify for *Levine*'s "clear evidence" exception. As the Court explained in *Mensing*, the exception requires a manufacturer "to *show, by 'clear*

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[29] Merck's quotation regarding "conflicting" literature is from the Merritt memorandum. *Compare* Pet.App.17a *with* JA766-67.

evidence,' that the FDA would have rescinded any change in the label." 564 U.S. at 624 n.8 (emphasis added). The Court's identification of "clear evidence" as the nature of the "show[ing]" required is consistent with a heightened standard of proof.

Such a heightened standard is justified because the "clear evidence" exception recognized in *Levine* stretches the bounds of impossibility preemption. Impossibility preemption typically applies "where it is 'impossible for a private party to comply with both state and federal requirements.'" *Id.* at 618 (quoting *Freightliner*, 514 U.S. at 287). But the FDCA and the CBE regulation make it "physically possible" for brand-name drug manufacturers "to provide stronger warnings." *Levine*, 555 U.S. at 591 (Thomas, J., concurring in the judgment). The "clear evidence" defense depends on a supposition that, *if* the manufacturer complies with state law, a federal agency will take action *in the future* that will prevent the manufacturer from continuing to comply with state law. Because "the possibility of impossibility" is "not enough" for preemption, *Mensing*, 564 U.S. at 624 n.8, a manufacturer must present a particularly compelling showing to trigger preemption under the "clear evidence" exception.

In any event, because it is undisputed that a clear showing is required, *see supra* p. 31 & n.14, it makes no difference whether such a showing is equivalent to the clear-and-convincing-evidence standard of evidentiary proof. The government contends (at 26) that, in the preemption context, "clear evidence" "reflect[s] an *interpretive* presumption against preemption." For its part, Merck concedes (at 46) that "courts should not lightly assume that the FDA would have rejected a proposed warning." It is hard to imagine a case that

would turn on whether the defense requires proof by clear-and-convincing evidence, or evidence sufficient to overcome an "interpretive presumption against preemption." Given Merck's feeble evidentiary showing, this case certainly does not. *See supra* Part II.

C. Granting Summary Judgment Would Violate Respondents' Procedural Rights

In all events, the district court's judgment could not be affirmed without considering respondents' challenge to that court's extraordinary decision to grant an order to show cause why all respondents' claims were not preempted on the basis of the *Glynn* advisory opinion.

Summary judgment must "be refused where the nonmoving party has not had the opportunity to discover information that is essential to his opposition." *Anderson*, 477 U.S. at 250 n.5. Here, the district court granted summary judgment after issuing a show-cause order giving respondents just 45 days to mount evidence in opposition to preemption. JA86-88.[30] The district court's conclusion (at Pet.App.136a) that such a compressed time frame was sufficient because the Glynns had the opportunity to brief preemption on a normal schedule was erroneous. Respondents were not parties in *Glynn*, and Ms. Glynn, who the jury found did not suffer an atypical femoral fracture, JA45, was hardly an adequate representative to litigate the viability of respondents' claims. Denying respondents a chance to gather evidence on the basis of *Glynn*, and applying the *Glynn* ruling against respondents with minimal analysis, violates "the

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[30] *See* JA91 (attorney declaration that 45-day window did not allow "the overwhelming majority of these Plaintiffs to pursue any case specific discovery" and that respondents would have gathered more evidence "if additional time had been provided").

'deep-rooted historic tradition that everyone should have his own day in court.'" *Taylor v. Sturgell*, 553 U.S. 880, 892-93 (2008) (quoting *Richards v. Jefferson Cty.*, 517 U.S. 793, 798 (1996)). The fact that *Glynn* was an MDL bellwether case does not mitigate that unfairness because a bellwether trial is not a "'representative' proceeding." Eldon E. Fallon et al., *Bellwether Trials in Multidistrict Litigation*, 82 Tul. L. Rev. 2323, 2332 (2008).[31]

Subsequent proceedings have starkly demonstrated the prejudice suffered by respondents. As Merck argued on appeal, its "single best piece of evidence" is the Merritt memorandum. Pet.App.49a n.125; JA764-67. Yet respondents have not had the opportunity to depose Merritt to test her credibility or the veracity of her notes.[32]

Although the Third Circuit did not need to reach respondents' objections to the show-cause procedure, the district court's judgment could not be upheld without addressing the procedural infirmities in the district court's approach.

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[31] *See also* Martin H. Redish & Julie M. Karaba, *One Size Doesn't Fit All: Multidistrict Litigation, Due Process, and the Dangers of Procedural Collectivism*, 95 B.U. L. Rev. 109, 126 (2015) (bellwether trials "are not binding on other parties in the MDL").

[32] More than 200 respondents were injured after the May 2009 Complete Response Letter, and some as late as September 2010. MDL Dkt. 2857-2. Those respondents could argue that, even if the Court accepts Merck's contentions regarding the Complete Response Letter, Merck could have warned of atypical femoral fractures at some point after the Complete Response Letter, but soon enough to prevent their injuries. However, the district court's schedule did not permit the type of plaintiff-specific discovery (e.g., when the warning would have been heeded) necessary to develop such an argument.

* * *

Federal law made it possible for Merck to comply with its state-law duty to warn adequately of atypical femoral fractures through a CBE supplement. Neither FDA's rejection of a very different stress-fracture warning, nor the informal FDA communications cited by Merck, established the clear evidence of impossibility required by this Court's precedents.

CONCLUSION

The judgment of the Third Circuit should be affirmed.

Respectfully submitted,

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1. The Supremacy Clause of the U.S. Constitution, art. VI, cl. 2, provides:

> This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.

2. 21 U.S.C. § 331 provides, in relevant part:

§ 331. Prohibited acts

The following acts and the causing thereof are prohibited:

(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.

* * *

3. 21 U.S.C. § 352 provides, in relevant part:

§ 352. Misbranded drugs and devices

A drug or device shall be deemed to be misbranded—

(a) False or misleading label

(1) If its labeling is false or misleading in any particular. Health care economic information provided to a payor, formulary committee, or other similar

entity with knowledge and expertise in the area of health care economic analysis, carrying out its responsibilities for the selection of drugs for coverage or reimbursement, shall not be considered to be false or misleading under this paragraph if the health care economic information relates to an indication approved under section 355 of this title or under section 262(a) of title 42 for such drug, is based on competent and reliable scientific evidence, and includes, where applicable, a conspicuous and prominent statement describing any material differences between the health care economic information and the labeling approved for the drug under section 355 of this title or under section 262 of title 42. The requirements set forth in section 355(a) of this title or in subsections (a) and (k) of section 262 of title 42 shall not apply to health care economic information provided to such a payor, committee, or entity in accordance with this paragraph. Information that is relevant to the substantiation of the health care economic information presented pursuant to this paragraph shall be made available to the Secretary upon request.

(2)(A) For purposes of this paragraph, the term "health care economic information" means any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug. Such analysis may be comparative to the use of another drug, to another health care intervention, or to no intervention.

(B) Such term does not include any analysis that relates only to an indication that is not approved under section 355 of this title or under section 262 of title 42 for such drug.

* * *

4. 21 U.S.C. § 355 provides, in relevant part:

§ 355. New drugs

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title. The applicant shall file with the application the patent

number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

* * *

(*o*) Postmarket studies and clinical trials; labeling

(1) In general

A responsible person may not introduce or deliver for introduction into interstate commerce the new drug involved if the person is in violation of a requirement established under paragraph (3) or (4) with respect to the drug.

(2) Definitions

For purposes of this subsection:

(A) Responsible person

The term "responsible person" means a person who—

(i) has submitted to the Secretary a covered application that is pending; or

(ii) is the holder of an approved covered application.

(B) Covered application

The term "covered application" means—

(i) an application under subsection (b) for a drug that is subject to section 353(b) of this title; and

(ii) an application under section 262 of title 42.

(C) New safety information; serious risk

The terms "new safety information", "serious risk", and "signal of a serious risk" have the meanings given such terms in section 355-1(b) of this title.

* * *

(4) Safety labeling changes requested by Secretary

(A) New safety information

If the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug, the Secretary shall promptly notify the responsible person or, if the same drug approved under subsection (b) is not currently marketed, the holder of an approved application under subsection (j).

(B) Response to notification

Following notification pursuant to subparagraph (A), the responsible person or the holder of the approved application under subsection (j) shall within 30 days—

(i) submit a supplement proposing changes to the approved labeling to reflect the new safety information, including changes to boxed warnings, contraindications, warnings, precautions, or adverse reactions; or

(ii) notify the Secretary that the responsible person or the holder of the approved application under subsection (j) does not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted.

(C) Review

Upon receipt of such supplement, the Secretary shall promptly review and act upon such supplement. If the Secretary disagrees with the proposed changes in the supplement or with the statement setting forth the reasons why no labeling change is necessary, the Secretary shall initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes.

(D) Discussions

Such discussions shall not extend for more than 30 days after the response to the notification under subparagraph (B), unless the Secretary determines an extension of such discussion period is warranted.

(E) Order

Within 15 days of the conclusion of the discussions under subparagraph (D), the Secretary may issue an order directing the responsible person or the holder of the approved application under subsection (j) to make such a labeling change as the Secretary deems appropriate to address the new safety information. Within 15 days of such an order, the responsible person or the holder of the approved application under subsection (j) shall submit a supplement containing the labeling change.

(F) Dispute resolution

Within 5 days of receiving an order under subparagraph (E), the responsible person or the holder of the approved application under subsection (j) may appeal using dispute resolution procedures established by the Secretary in regulation and guidance.

(G) Violation

If the responsible person or the holder of the approved application under subsection (j) has not submitted a supplement within 15 days of the date of such order under subparagraph (E), and there is no appeal or dispute resolution proceeding pending, the responsible person or holder shall be considered to be in violation of this subsection. If at the conclusion of any dispute resolution procedures the Secretary determines that a supplement must be submitted and such a supplement is not submitted within 15 days of the date of that determination, the responsible person or holder shall be in violation of this subsection.

(H) Public health threat

Notwithstanding subparagraphs (A) through (F), if the Secretary concludes that such a labeling change is necessary to protect the public health, the Secretary may accelerate the timelines in such subparagraphs.

(I) Rule of construction

This paragraph shall not be construed to affect the responsibility of the responsible person or the holder of the approved application under subsection (j) to maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations).

* * *

5. 21 U.S.C. § 360k provides, in relevant part:

§ 360k. State and local requirements respecting devices

(a) General rule

Except as provided in subsection (b), no State or political subdivision of a State may establish or continue in effect with respect to a device intended for human use any requirement—

(1) which is different from, or in addition to, any requirement applicable under this chapter to the device, and

(2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under this chapter.

* * *

6. Section 202 of the Drug Amendments of 1968, Pub. L. No. 87-781, 76 Stat. 780, 793, provides:

Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law.

7. 21 C.F.R. § 201.57 provides, in relevant part:

§ 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).

The requirements in this section apply only to prescription drug products described in § 201.56(b)(1) and must be implemented according to the schedule specified in § 201.56(c), except for the requirement in paragraph (c)(18) of this section to reprint any FDA-approved patient labeling at the end of prescription drug labeling or accompany the prescription drug labeling, which must be implemented no later than June 30, 2007.

(a) *Highlights of prescribing information.* The following information must appear in all prescription drug labeling:

* * *

(6) *Indications and usage.* A concise statement of each of the product's indications, as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. If the product is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class in the following manner: "(Drug) is a (name of class) indicated for (indication(s))."

* * *

(9) *Contraindications.* A concise statement of each of the product's contraindications, as required under paragraph (c)(5) of this section, with any appropriate subheadings.

(10) *Warnings and precautions.* A concise summary of the most clinically significant information required under paragraph (c)(6) of this section, with any appropriate subheadings, including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm.

(11) *Adverse reactions.* (i) A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., incidence rate). Adverse reactions important for other reasons (e.g.,

because they are serious or frequently lead to discontinuation or dosage adjustment) must not be repeated under this heading in Highlights if they are included elsewhere in Highlights (e.g., Warnings and Precautions, Contraindications).

(ii) For drug products other than vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or FDA at (*insert current FDA phone number and Web address for voluntary reporting of adverse reactions*)."

(iii) For vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or VAERS at (*insert the current VAERS phone number and Web address for voluntary reporting of adverse reactions*)."

(iv) For manufacturers with a Web site for voluntary reporting of adverse reactions, the Web address of the direct link to the site.

* * *

(b) *Full prescribing information: Contents.* Contents must contain a list of each heading and subheading required in the full prescribing information under § 201.56(d)(1), if not omitted under § 201.56(d)(4), preceded by the identifying number required under § 201.56(d)(1). Contents must also contain any additional subheading(s) included in the full prescribing information preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(c) *Full prescribing information.* The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings,

subheadings, and identifying numbers required under § 201.56(d)(1), unless omitted under § 201.56(d)(4). If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(1) *Boxed warning.* Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.

(2) *1 Indications and usage.* This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

(i) This section must include the following information when the conditions listed are applicable:

* * *

(F) If there are specific conditions that should be met before the drug is used on a long term basis (e.g., demonstration of responsiveness to the drug in a short term trial in a given patient), a statement of the conditions; or, if the indications for long term use are

different from those for short term use, a statement of the specific indications for each use.

* * *

(3) *2 Dosage and administration.* (i) This section must state the recommended dose and, as appropriate:

* * *

(F) The usual duration of treatment when treatment duration should be limited,

* * *

(6) *5 Warnings and precautions.* (i) *General.* This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance

with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

(ii) *Other special care precautions.* This section must contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (e.g., precautions not required under any other specific section or subsection).

(iii) *Monitoring: Laboratory tests.* This section must identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information must be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be performed before, during, and after therapy.

(iv) *Interference with laboratory tests.* This section must briefly note information on any known interference by the product with laboratory tests and reference the section where the detailed information is presented (e.g., "Drug Interactions" section).

(7) *6 Adverse reactions.* This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

(i) *Listing of adverse reactions.* This section must list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. The list or lists must be preceded by the information necessary to interpret the adverse reactions (e.g., for clinical trials, total number exposed, extent and nature of exposure).

(ii) *Categorization of adverse reactions.* Within a listing, adverse reactions must be categorized by body system, by severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency information cannot be reliably determined, adverse reactions must be listed in decreasing order of severity.

(A) *Clinical trials experience.* This section must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing. If comparative rates of occurrence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined. For adverse

reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.

(B) *Postmarketing experience.* This section of the labeling must list the adverse reactions, as defined in paragraph (c)(7) of this section, that are identified from domestic and foreign spontaneous reports. This listing must be separate from the listing of adverse reactions identified in clinical trials.

(iii) *Comparisons of adverse reactions between drugs.* For drug products other than biological products, any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions must be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, any such claim must be based on substantial evidence.

* * *

(d) *Format requirements.* All labeling information required under paragraphs (a), (b), and (c) of this section must be printed in accordance with the following specifications:

(1) All headings and subheadings required by paragraphs (a) and (c) of this section must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Reverse type is not permitted as a form of highlighting.

(2) A horizontal line must separate the information required by paragraphs (a), (b), and (c) of this section.

(3) The headings listed in paragraphs (a)(5) through (a)(13) of this section must be presented in the center of a horizontal line.

(4) If there are multiple subheadings listed under paragraphs (a)(4) through (a)(13) of this section, each subheading must be preceded by a bullet point.

(5) The labeling information required by paragraphs (a)(1) through (a)(4), (a)(11)(ii) through (a)(11)(iv), and (a)(14) of this section must be in bold print.

(6) The letter height or type size for all labeling information, headings, and subheadings set forth in paragraphs (a), (b), and (c) of this section must be a minimum of 8 points, except for labeling information that is on or within the package from which the drug is to be dispensed, which must be a minimum of 6 points.

(7) The identifying numbers required by § 201.56(d) and paragraphs (c)(1) through (c)(18) of this section must be presented in bold print and must precede the heading or subheading by at least two square em's (i.e., two squares of the size of the letter "m" in 8 point type).

(8) The information required by paragraph (a) of this section, not including the information required under paragraph (a)(4) of this section, must be limited in length to an amount that, if printed in 2 columns on a standard sized piece of typing paper (8½ by 11 inches), single spaced, in 8 point type with ½-inch margins on all sides and between columns, would fit on one-half of the page.

(9) Sections or subsections of labeling that are identified as containing recent major changes under paragraph (a)(5) of this section must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the new or modified text.

(10) For the information required by paragraph (b) of this section, each section heading must be in bold print. Each subheading within a section must be indented and not bolded.

8. 21 C.F.R. § 314.3 provides, in relevant part:

§ 314.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act apply to those terms when used in this part and part 320 of this chapter.

(b) The following definitions of terms apply to this part and part 320 of this chapter:

* * *

Newly acquired information is data, analyses, or other information not previously submitted to the Agency, which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

* * *

9. 21 C.F.R. § 314.70 provides, in relevant part:

§ 314.70 Supplements and other changes to an approved NDA.

(a) *Changes to an approved NDA.* (1)(i) Except as provided in paragraph (a)(1)(ii) of this section, the applicant must notify FDA about each change in each condition established in an approved NDA beyond the variations already provided for in the NDA. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about the change in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the NDA under paragraph (d) of this section.

(ii) The submission and grant of a written request for an exception or alternative under § 201.26 of this chapter satisfies the applicable requirements in paragraphs (a) through (c) of this section. However, any grant of a request for an exception or alternative under § 201.26 of this chapter must be reported as part of the annual report to the NDA under paragraph (d) of this section.

(2) The NDA holder must assess the effects of the change before distributing a drug product made with a manufacturing change.

(3) Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) and (c) of this section.

(5) Except for a supplement providing for a change in the labeling, the applicant must include in each supplement and amendment to a supplement providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy has been provided in accordance with § 314.440(a)(4).

(6) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the submission.

(b) *Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).* (1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

(2) These changes include, but are not limited to:

* * *

(v) The following labeling changes:

(A) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

(B) If applicable, any change to a Medication Guide required under part 208 of this chapter, except

for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter; and

(C) Any change to the information required by § 201.57(a) of this chapter, with the following exceptions that may be reported in an annual report under paragraph (d)(2)(x) of this section:

(*1*) Removal of a listed section(s) specified in § 201.57(a)(5) of this chapter; and

(*2*) Changes to the most recent revision date of the labeling as specified in § 201.57(a)(15) of this chapter.

* * *

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using a change under paragraph (b) of this section. Except for submissions under paragraph (e) of this section, the following information must be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The drug product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to assess the effects of the change;

(v) The data derived from such studies;

* * *

(c) *Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).* (1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the

identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

* * *

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement—Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved NDA may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

* * *

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental NDA, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

* * *

10. 21 C.F.R. § 314.71 provides:

§ 314.71 Procedures for submission of a supplement to an approved application.

(a) Only the applicant may submit a supplement to an application.

(b) All procedures and actions that apply to an application under § 314.50 also apply to supplements, except that the information required in the supplement is limited to that needed to support the change. A supplement is required to contain an archival copy and a review copy that include an application form and appropriate technical sections, samples, and labeling; except that a supplement for a change other than a change in labeling is required also to contain a field copy.

(c) All procedures and actions that apply to applications under this part, including actions by applicants and the Food and Drug Administration, also apply to supplements except as specified otherwise in this part.

11. 21 C.F.R. § 314.102 provides, in relevant part:

§ 314.102 Communications between FDA and applicants.

(a) *General principles.* During the course of reviewing an application or an abbreviated application, FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process. Such communication may take the form of telephone conversations, letters, or meetings, whichever is most appropriate to discuss the particular issue at hand. Communications shall be appropriately documented in the application in accordance with § 10.65 of this chapter. Further details on the procedures for communication between FDA and applicants are contained in a staff manual guide that is publicly available.

(b) *Notification of easily correctable deficiencies.* FDA reviewers shall make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application or an abbreviated application when those deficiencies are discovered, particularly deficiencies concerning chemistry, manufacturing, and controls issues. The agency will also inform applicants promptly of its need for more data or information or for technical changes in the application or the abbreviated application needed to facilitate the agency's review. This early communication is intended to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed. Such early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application or abbreviated application by agency

managers as well as reviewing staff. Instead, major scientific issues will ordinarily be addressed in a complete response letter.

12. 21 C.F.R. § 314.105 provides, in relevant part:

§ 314.105 Approval of an NDA and an ANDA.

* * *

(b) FDA will approve an NDA and issue the applicant an approval letter on the basis of draft labeling if the only deficiencies in the NDA concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.

* * *

13. 21 C.F.R. § 314.110 provides:

§ 314.110 Complete response letter to the applicant.

(a) *Complete response letter.* FDA will send the applicant a complete response letter if the agency determines that we will not approve the application or abbreviated application in its present form for one or more of the reasons given in § 314.125 or § 314.127, respectively.

(1) *Description of specific deficiencies.* A complete response letter will describe all of the specific deficiencies that the agency has identified in an application or abbreviated application, except as stated in paragraph (a)(3) of this section.

(2) *Complete review of data.* A complete response letter reflects FDA's complete review of the data submitted in an original application or abbreviated application (or, where appropriate, a resubmission) and any amendments that the agency has reviewed. The complete response letter will identify any amendments that the agency has not yet reviewed.

(3) *Inadequate data.* If FDA determines, after an application is filed or an abbreviated application is received, that the data submitted are inadequate to support approval, the agency might issue a complete response letter without first conducting required inspections and/or reviewing proposed product labeling.

(4) *Recommendation of actions for approval.* When possible, a complete response letter will recommend actions that the applicant might take to place the application or abbreviated application in condition for approval.

(b) *Applicant actions.* After receiving a complete response letter, the applicant must take one of following actions:

(1) *Resubmission.* Resubmit the application or abbreviated application, addressing all deficiencies identified in the complete response letter.

(i) A resubmission of an application or efficacy supplement that FDA classifies as a Class 1 resubmission constitutes an agreement by the applicant to start a

new 2-month review cycle beginning on the date FDA receives the resubmission.

(ii) A resubmission of an application or efficacy supplement that FDA classifies as a Class 2 resubmission constitutes an agreement by the applicant to start a new 6-month review cycle beginning on the date FDA receives the resubmission.

(iii) A resubmission of an NDA supplement other than an efficacy supplement constitutes an agreement by the applicant to start a new review cycle the same length as the initial review cycle for the supplement (excluding any extension due to a major amendment of the initial supplement), beginning on the date FDA receives the resubmission.

(iv) A major resubmission of an abbreviated application constitutes an agreement by the applicant to start a new 6-month review cycle beginning on the date FDA receives the resubmission.

(v) A minor resubmission of an abbreviated application constitutes an agreement by the applicant to start a new review cycle beginning on the date FDA receives the resubmission.

(2) *Withdrawal.* Withdraw the application or abbreviated application. A decision to withdraw an application or abbreviated application is without prejudice to a subsequent submission.

(3) *Request opportunity for hearing.* Ask the agency to provide the applicant an opportunity for a hearing on the question of whether there are grounds for denying approval of the application or abbreviated application under section 505(d) or (j)(4) of the act, respectively. The applicant must submit the request to the Associate Director for Policy, Center for Drug

Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993. Within 60 days of the date of the request for an opportunity for a hearing, or within a different time period to which FDA and the applicant agree, the agency will either approve the application or abbreviated application under § 314.105, or refuse to approve the application under § 314.125 or abbreviated application under § 314.127 and give the applicant written notice of an opportunity for a hearing under § 314.200 and section 505(c)(1)(B) or (j)(5)(c) of the act on the question of whether there are grounds for denying approval of the application or abbreviated application under section 505(d) or (j)(4) of the act, respectively.

(c) *Failure to take action.* (1) An applicant agrees to extend the review period under section 505(c)(1) or (j)(5)(A) of the act until it takes any of the actions listed in paragraph (b) of this section. For an application or abbreviated application, FDA may consider an applicant's failure to take any of such actions within 1 year after issuance of a complete response letter to be a request by the applicant to withdraw the application, unless the applicant has requested an extension of time in which to resubmit the application. FDA will grant any reasonable request for such an extension. FDA may consider an applicant's failure to resubmit the application within the extended time period or to request an additional extension to be a request by the applicant to withdraw the application.

(2) If FDA considers an applicant's failure to take action in accordance with paragraph (c)(1) of this section to be a request to withdraw the application, the agency will notify the applicant in writing. The applicant will have 30 days from the date of the notification to explain why the application should not

be withdrawn and to request an extension of time in which to resubmit the application. FDA will grant any reasonable request for an extension. If the applicant does not respond to the notification within 30 days, the application will be deemed to be withdrawn.

14. 21 C.F.R. § 314.125 provides, in relevant part:

§ 314.125 Refusal to approve an NDA.

(a) The Food and Drug Administration will refuse to approve the NDA and for a new drug give the applicant written notice of an opportunity for a hearing under § 314.200 on the question of whether there are grounds for denying approval of the NDA under section 505(d) of the Federal Food, Drug, and Cosmetic Act, if:

(1) FDA sends the applicant a complete response letter under § 314.110;

(2) The applicant requests an opportunity for hearing for a new drug on the question of whether the NDA is approvable; and

(3) FDA finds that any of the reasons given in paragraph (b) of this section apply.

(b) FDA may refuse to approve an NDA for any of the following reasons, unless the requirement has been waived under § 314.90:

* * *

(6) The proposed labeling is false or misleading in any particular.

* * *

(8) The drug product's proposed labeling does not comply with the requirements for labels and labeling in part 201.

* * *

No. 17-290

IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,

Petitioner,

v.

DORIS ALBRECHT, ET AL.,

Respondents.

On Writ of Certiorari
To The United States Court of Appeals
For The Third Circuit

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INTRODUCTION

Respondents do not dispute that Merck shared the available scientific data with the FDA, proposed to warn about the risk of "low-energy femoral shaft fracture[s]," and was rebuffed by the FDA in a formal written response. Yet Respondents insist that Merck may be held liable for failure to warn under state tort law, because a jury might conclude—after holding Merck to an unjustifiably heightened burden of proof—that the FDA chose to keep doctors and patients in the dark about a genuine safety risk simply because it did not like Merck's choice of *terminology* for the type of fracture.

The law forecloses that speculation. Instead, it presumes that the FDA properly discharges its duties, including its statutory obligation to work with manufacturers on labeling changes when it becomes aware of new safety information. The FDA's conscious choice not to do so when confronted with a proposed revision and the relevant data thus establishes, as a matter of law, that the manufacturer could not have changed its label to comply with state law's purported demands.

Merck should still prevail even if the law allows courts to second-guess the FDA as Respondents insist. The FDA has now told this Court that it would not have allowed Merck to add a warning before September 2010, and that comports with every other known fact. There could hardly be any "clear[er] evidence that the FDA would not have approved" the changes state law demanded, *Wyeth v. Levine*, 555 U.S. 555, 571 (2009), particularly under the *ordinary* burden of proof.

ARGUMENT

I. THE FDA'S DENIAL OF MERCK'S PROPOSED WARNING PREEMPTS RESPONDENTS' CLAIMS AS A MATTER OF LAW.

Merck's argument is simple: When a drug manufacturer proposes warning about a risk and shares all the relevant scientific data, but the FDA responds with a "no," the manufacturer cannot be held liable for failure to warn about that risk. That is because the FDA's actual rejection legally establishes the impossibility of adding a warning. Any other conclusion ignores the FDA's statutory obligations and its own regulatory framework—as now confirmed by the United States. Respondents dispute this legal rule and deny that it applies here; they are wrong in both respects.

A. Failure-To-Warn Claims Are Preempted When the FDA Rejects a Proposed Warning About a Disclosed Risk.

All parties agree that if the FDA prevented or "would have prevented" a drug manufacturer "from adding a stronger warning," state-law claims based on a failure to do so are preempted. *Levine*, 555 U.S. at 573; *see* Resp. Br. 30. The question is how to prove that condition. Merck's point is that, as a matter of law, the agency "would have prevented" a warning if, after being informed of the relevant risk, the agency prevented a proposed warning about it.

This follows from the governing statutory and regulatory regime. When the FDA "becomes aware of new safety information"—including information provided by a manufacturer—"that [it] determines should be included in the labeling," the FDA "*shall*

promptly notify" the manufacturer, seek a response, and then "promptly review and act upon" that response. 21 U.S.C. § 355(*o*)(4)(A)–(C) (emphasis added). And under FDA regulations, a proposed labeling change may be rejected only if it is deficient in substance, not just in semantics. *See* 21 C.F.R. § 314.102(b) (FDA must make "every reasonable effort" to communicate "easily correctable deficiencies"); *id.* § 314.105(b) (if a proposal's "only deficiencies ... concern editorial or similar minor deficiencies in the draft labeling," FDA will conditionally approve). The FDA interprets these rules the same way. *See* U.S. Br. 32–33.

Given the presumption of regularity afforded to the FDA's conduct, the agency's informed decision to reject a proposal shows that it did not believe the risk justified a warning. Otherwise, it would have honored its obligations under § 355(*o*)(4) and worked with the manufacturer toward mutually acceptable revisions. Similarly, it would have honored its own regulatory promise to smooth over "editorial or similar minor deficiencies in the draft labeling," such as by suggesting alternative language. If it did not do so, and instead rejected the proposal, the law permits only one conclusion: The FDA did not permit the manufacturer to warn about the risk in question, and thus, at that time, would not have permitted any new warning about that risk. In other words, it would have been impossible to warn about the relevant risk without contradicting the FDA, in violation of federal law. The FDA does not put patient health and informed consent in jeopardy by rejecting scientifically justified warnings simply

because it disagrees with a manufacturer's proposed phrasing. Again, the FDA agrees. U.S. Br. 31–33.

This rule makes good sense. Because all agree that determining the meaning and effect of the FDA's complete response letter is a question for the court, this rule avoids the specter of numerous juries deploying their "intuitions" about "administrative inertia and agency decision-making processes" to decide preemption. Pet.App.54a. It also places the relevant burdens on the right shoulders. Manufacturers, for their part, must monitor scientific developments and seek a label change if necessary. But the FDA retains the final word—without later second-guessing—about patient health and public safety.

Respondents and their amici dispute this rule on several fronts, but their arguments fail.

1. Respondents and their amici start with a straw-man: that, on Merck's view, manufacturers may never be liable for failure to warn, because it is the FDA's obligation to "mandate a label change," and so the agency's inaction alone suffices to establish impossibility. Resp. Br. 31–34; *e.g.*, Pub. Citizen Br. 11–12. That theory—essentially, that the enactment of § 355(*o*)(4) in 2007 abrogated *Levine*—is not (and has never been) Merck's argument.

Even after the amendments, the "manufacturer retains the responsibility 'to maintain its label in accordance with existing requirements.'" *Levine*, 555 U.S. at 571 (quoting § 355(*o*)(4)(I)). And, even after the amendments, a court cannot presume that the FDA, with its "limited resources to monitor the 11,000 drugs on the market" and inferior "access to

information" about emerging safety risks, has reviewed the scientific data and passed judgment on the propriety of warning about every possible risk. *Id.* at 578–79. That is why, even after the amendments, the law does not "insulate manufacturers from liability or authorize them to wait to act until mandated by FDA." Resp. Br. 34.

Merck's point is different: Once a manufacturer discharges its duty by bringing a specific risk to the FDA's attention and proposing to warn about it, the agency's denial of that proposal must be understood in light of the duties imposed by the 2007 statutory amendments. The amendments do not change the allocation of duties between manufacturer and regulator. But they do inform our understanding of what it means when the regulator speaks: When an informed regulator formally rejects a proposal to warn of a risk, that ends the matter.

Respondents' amici make a similar error, worrying that, under Merck's rule, the FDA's rejection of a warning means that failure-to-warn claims based on that risk are preempted forever. *E.g.*, Virginia Br. 12. That too is incorrect. If new, material information emerges after the agency's decision, that decision is no longer conclusive; the question under those circumstances would be whether the FDA would have reconsidered in light of that new evidence. But since Respondents point to no new evidence during the relevant period, this case does not present that question.

2. Respondents also contend that § 355(*o*)(4)'s duty is entirely "*discretionary*," so that one cannot infer anything from the FDA's rejection of a proposed warning. Resp. Br. 32. Perhaps the FDA agrees that

the science justifies a new warning but dislikes the manufacturer's phrasing and, exercising its supposed discretion, declines to start a discussion with the manufacturer. If so, Respondents say, then federal law would not have precluded the manufacturer from adding a different warning satisfactory to the FDA.

Respondents' premise is wrong. The word "shall" does not mean "may." To the contrary, the "word 'shall' usually creates a mandate, not a liberty." *Murphy v. Smith*, 138 S. Ct. 784, 787 (2018). So, when § 355(*o*)(4) says that the FDA "shall" initiate a process to modify the labeling when it learns of new information that it believes should be added to the label, it imposes a "nondiscretionary duty" to start that process upon receiving the information. *Id.* The FDA's failure to initiate that process therefore necessarily implies the lack of information that, in its view, justifies a warning.

Respondents' lone citation—*United States v. George S. Bush & Co.*, 310 U.S. 371 (1940)—does not support their unnatural reading of "shall." There, the Tariff Act of 1930 provided that the President "shall by proclamation approve the rates" recommended by the Tariff Commission "*if in his judgment* such rates ... are shown ... to be necessary." *Id.* at 376–77 (emphasis added). The Court held that the statute, by instructing the President to exercise "his judgment" in deciding if a tariff is "necessary," left him with discretion over how to determine necessity. *See id.* at 379–80. The Court never considered the meaning of "shall"—and certainly never hinted that "shall" means "may," so that the President could decline to approve a recommended tariff even after finding it "necessary."

To be sure, § 355(*o*)(4) directs the FDA to begin a label-changing process only if the FDA "determines" that the new information "should be included in the labeling." But it is precisely the FDA's judgment and belief that controls the preemption inquiry, because adding a warning is legally impossible unless the FDA agrees to it. If the agency declines to initiate a § 355(*o*)(4) process, that means it does not believe the new information justifies a new warning—and *that* clearly demonstrates the impossibility of adding such a warning.

3. Respondents and their amici next point out that, long before the plaintiff in *Levine* was injured, the FDA rejected a proposal by Wyeth to change its label on intravenous injection. *See* Resp. Br. 38; Tort Law Professors Br. 21–23; MedShadow Found. Br. 21. If Merck were right, their argument seems to go, then *Levine* should have come out the other way.

Of course, Congress passed § 355(*o*)(4) "after Levine's injury and lawsuit." 555 U.S. at 567. So, *Levine* properly did not consider its effect when deciding what to make of the FDA's decade-earlier decision to reject Wyeth's proposal. *Levine* would have been a poor case in which to address the effect of a previous denial anyway. The majority there found that Wyeth's proposal—which came *twelve years* before Levine's injury, and thus assuredly did not reflect all the available evidence as of the latter date—"did not differ in any material respect from the FDA-approved warning" that was inadequate. 555 U.S. at 572 n.5. Hence the Court's conclusion that the FDA had never "made an affirmative decision" on the central issue. *Id.* at 573.

4. Finally, one of Respondents' amici objects that the FDA's rejection of Merck's proposal is mere "agency action," which (unlike "laws" and "treaties") carries no preeemptive force under the Supremacy Clause. Cato Inst. Br. 1. That misses the point. It is not *the FDA's rejection* that preempts Respondents' claims. It is *§ 355*—undeniably among the "laws of the United States"—which prohibits the sale of drugs without an FDA-approved label. The FDA's rejection matters only because it proves the impossibility of issuing an FDA-approved label that includes the state-mandated warning. "Many other federal statutes preempt state law" in similar fashion, and this Court unanimously upheld one against an identical Supremacy Clause challenge just two terms ago. *Coventry Health Care of Mo., Inc. v. Nevils*, 137 S. Ct. 1190, 1198 (2017); *id.* at 1199 (Thomas, J., concurring) (writing separately to note that such laws must constrain executive discretion to avoid improper delegation).

B. This Legal Rule Preempts Respondents' Claims Here.

Under this legal rule, Respondents' claims are preempted. There is no dispute on the three key predicates. *First*, Merck "kept the FDA informed" of "scores of case studies, reports, and articles ... documenting possible," albeit uncertain, "connections between long-term bisphosphonate use and atypical femoral fractures." Pet.App.13a; *see also* Pet.App.13a–14a. *Second*, after the FDA told Merck that it was "concerned about this developing safety signal," Pet.App.14a, Merck proposed a Precaution to "address atypical femoral fractures," Pet.App.15a—that is, addressed to "[l]ow-energy fractures of the

subtrochanteric and proximal femoral shaft," J.A.707. *Third*, the FDA rejected that proposal. J.A. 510–13. It follows that it was impossible for Merck to have warned about those fractures before September 2010, when the FDA revisited the issue in light of the intervening task force report.

Respondents object to this application of law to fact in two respects. *First*, they contend that Merck "never proposed a warning of atypical femoral fractures to FDA," because its proposal concerned a (supposedly) different injury—"stress fractures." Resp. Br. 35. *Second*, they argue that the FDA did not *really* reject Merck's proposal. Resp. Br. 40. Neither argument withstands even minimal scrutiny.

1. Respondents insist that because Merck's warning mentioned "stress fractures" several times, Merck sought to warn only about minor injuries suffered by (for example) new joggers, not the atypical femoral fractures that injured Respondents. Resp. Br. 36–38. This Court presumably rejected that revisionist history in granting certiorari. *See* BIO 18–19. It should do so again.

No one could reasonably believe that Merck was trying to warn about anything besides the type of injuries that Respondents suffered—or that the FDA was confused about that. Take first the proposed label itself. Its *title* addressed "low-energy femoral shaft fracture[s]." J.A.707 (capitalization altered). Its first sentence reiterated that focus, addressing "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft," *id.*—the definition of atypical femoral fractures, not just a name.

The rest of Merck's proposed label followed suit. As Respondents' expert and amici note, atypical femoral fractures have two distinctive characteristics: they are "insufficiency" fractures (meaning they occur with normal activity on bones of abnormally decreased density), and they often progress to "complete" fracture (meaning the bone is split all the way through). *E.g.*, J.A.100, 136; Lane Br. 9–10, 18. Merck's proposed label identified both of those characteristics: some of the "insufficiency fractures" in question had progressed to "complete fracture." J.A.707. And the rest of Merck's application further made clear that Merck was talking about atypical femoral fractures. *E.g.*, J.A.748 (noting reports of "low-energy subtrochanteric / mid femoral shaft fractures"); J.A.753 (noting that, of 65 reports that included "information on fracture management," the six patients with "incomplete" fractures were "treated conservatively" while the 59 others had "surg[ery]"); J.A.746 (noting that some of these "insufficiency" fractures were caused by "normal" activity). Given these materials, it defies belief to think that Merck was talking about something categorically different when it proposed its warning.

To be sure, the proper terminology for these fractures was unsettled in 2008, but they were often referred to as stress or insufficiency fractures. *Compare, e.g.*, S.K. Goh et al., *Subtrochanteric Insufficiency Fractures in Patients on Alendronate Therapy*, 89 J. Bone & Joint Surgery 349 (2007) (cited in the FDA's request for additional information, J.A.281), *with* E.B. Kwek et al., *An Emerging Pattern of Subtrochanteric Stress*

Fractures: A Long-Term Complication of Alendronate Therapy?, Injury, Feb. 2008, at 224–231. Indeed, the very expert task force with whom the FDA worked to evaluate the issue confirmed that atypical fractures "*are* stress fractures" whose ordinary healing may be interrupted by the "suppression of remodeling" that is associated with long-term bisphosphonate use. Elizabeth Shane et al., *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society for Bone and Mineral Research*, 29 J. Bone & Min. Res. 1, 12 (2014) (emphasis added). At a bare minimum, even Respondents' expert and amici concede that atypical femoral fractures "start as ... stress fracture[s]." Lane Br. 12; *e.g.*, J.A.145 (claiming that Fosamax "allow[s] the initial stress fracture lesion to continue to grow until complete fracture").

In any event, the way Merck used this term was clear from the face of its application, as Merck explained that choice in its proposal. *See, e.g.*, J.A.670 ("Merck is proposing to add language ... to describe low-energy fractures that have been reported, of which some have been stress/insufficiency fractures"). While the FDA ultimately concluded (among other things) that Merck's discussion of stress fractures might cause confusion, it always recognized—indeed, it has affirmatively stated—that Merck tried to warn about atypical femoral fractures. *See* U.S. Br. 30 (the "exact same risk"). In short, whatever the merits of Merck's terminology, everyone knew what it was talking about—especially the FDA.

Respondents note that the "FDA and Merck have acknowledged the crucial distinction between stress

fractures and atypical femoral fractures," and point to a (later) 2010 exchange during which the FDA removed a reference to "stress fractures" from Merck's suggested revisions to the FDA's proposal. Resp. Br. 36; *see* J.A.566. This proves *Merck's* point: Merck's terminology did not confuse the FDA; rather, the FDA understood precisely the risk that Merck was seeking to warn about.

Finally, Respondents object that Merck's proposed warning "obscured the nature of atypical femoral fractures," by failing to explain "the scientific mechanism" by which Fosamax causes them, and by noting that similar fractures had also occurred prior to the availability of bisphosphonates. Resp. Br. 37–38. Neither point has any legal relevance, since (as explained) there is no claim that Merck concealed any material information from the FDA, and no plausible concern that the FDA misunderstood the nature of the risk at issue. Regardless, both of Respondents' complaints fail on their own terms. The scientific process by which Fosamax may contribute to atypical femoral fractures had been well-documented in "scores of case studies, reports, and articles" dating back years, Pet.App.13a, and Merck's PAS cited those at length, J.A.748–49. And while these types of fractures are "*predominantly* seen in bisphosphonate users," Resp. Br. 37–38 (emphasis added), Respondents' qualifier gives away the game. To this day, Fosamax's FDA-approved label informs doctors that "these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates"—because they do. J.A.223. In neither respect did Merck mislead the FDA at all, much less in a legally material way.

2. Despite conceding in the Third Circuit that the FDA's rejection of Merck's proposal was "final, written regulatory action[]," Resp. CA3 Letter, at 3, Respondents now insist that the FDA did not *really* reject Merck's proposal. Pointing out that the FDA's complete response letter told Merck that it was free to "resubmit" the application if it did not wish to withdraw it, Respondents argue that Merck could have resubmitted a revised warning by filing a new PAS or through the CBE process. Resp. Br. 40; *see also* Pub. Law Scholars Br. 17–18.

Of course it is true that Merck had the technical right to refile its proposal or to engage the CBE process, and the FDA acknowledged as much in boilerplate language. But that hardly matters if the FDA would have rejected a resubmitted warning. As explained above, it clearly would have. The statute and the FDA's own regulations required the agency to take specific steps if it determined that a warning was warranted. Its failure to do so thus shows its determination that a warning was *not* warranted at that time, based on the complete scientific data that Merck provided to it. And that determination, in turn, makes plain that the FDA would not have suddenly turned around and approved a resubmitted warning about the same risk, based on the same data—whether Merck sought permission (under the PAS process) or forgiveness (under the CBE process). Indulging in Respondents' contrary speculation would make it impossible *ever* to prove impossibility preemption. *See PLIVA, Inc. v. Mensing*, 564 U.S. 604, 623 (2011) (plurality op.) (warning against denying preemption based on "speculation").

II. MERCK PREVAILS IN THIS CASE UNDER ANY LEGAL FRAMEWORK.

The rule set forth above, focused on the meaning and effect of the FDA's actual decision, provides the cleanest way to resolve this case and provide helpful guidance in this confused area of the law. But even without that rule, Respondents' claims are still preempted. The FDA has now unambiguously told this Court that it rejected Merck's proposal on scientific grounds and therefore would not have approved *any* warning about atypical femoral fractures before the task force published its report in September 2010. That dispositive representation simply corroborates what the undisputed record already showed, despite Respondents' distractions. Indeed, the Third Circuit overcame the force of that record only by adopting a clear-and-convincing standard of proof that Respondents only half-heartedly defend.

A. The FDA Has Told This Court That It Would Not Have Approved a Warning.

Everyone agrees that Merck wins if it has "clear evidence that the FDA would not have approved" the warning supposedly required by state law. *Levine*, 555 U.S. at 571; *see* Resp. Br. 30. Even if the denial of Merck's proposal, standing alone, does not satisfy that test as a matter of law, other evidence does.

The United States has stated that the FDA "rejected a change to Fosamax's Warnings and Precautions because the data at that time was insufficient to justify a change." U.S. Br. 30 (capitalization altered). "It was only in October 2010—after an external task force had completed its

report on the issue—that FDA came to 'believe that the information' about atypical femoral fractures should be added to the Warnings and Precautions section." *Id.* at 33 (quoting J.A.527–28). It is hard to get clearer evidence than that.

Respondents insist, however, that these statements are merely "legal argument" from the Office of the Solicitor General. Resp. Br. 45. They then insist that the United States' views deserve no weight because "no regulation purportedly preempts state law" and because of growing skepticism about *Auer* deference. *Id.* at 45–46.

Wrong on both fronts. Respondents' first complaint seems to be that the United States' brief does not expressly state that the FDA agrees with its statements about Fosamax's regulatory history. But the United States' brief *is signed by* the FDA's parent agency, the Department of Health and Human Services. Respondents cannot seriously contend that the brief's statements about how the FDA operates and about how the FDA discharged its duties in acting on Merck's application do not reflect the FDA's views or representations.

Moreover, even if the United States' brief merely reflected the FDA's "legal argument" about its own actions, it still must "make a difference" in the preemption analysis. *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 883 (2000). Respondents concede that, had the FDA promulgated a *regulation* and explained its purposes (as in *Geier*), the FDA's views would be given "weight" in determining whether state law stands as an obstacle to federal law. Resp. Br. 45. They fail to explain why a much less problematic agency "interpretation"—its explanation

of why it rejected Merck's proposal and its view of the science at the time—deserves no weight in determining whether *the agency itself* "would not have approved" a change to Fosamax's label. *Levine*, 555 U.S. at 571. Who better to explain the FDA's actions than the FDA?

For similar reasons, the "equal protection concerns" arising from "regulat[ion] by *amicus* brief," Resp. Br. 46, are absent here. The United States' brief—which tracks its certiorari-stage amicus brief, filed upon invitation from the Court—is not an attempt at regulation, merely an explanation of FDA action. Accepting its explanation would not make it harder for "people to know if their conduct is permissible when they act." *E.I. du Pont de Nemours & Co. v. Smiley*, 138 S. Ct. 2563, 2564 (2018) (Gorsuch, J., respecting the denial of certiorari). Nor would it "incentiviz[e] agencies" to promulgate ambiguous regulations, *id.* at 2564, none of which is at issue here. Whatever the validity or vitality of the *Auer* doctrine, there is no reason to let juries second-guess the FDA's own unequivocal statement about what it would have done with a rephrased warning.

If the question whether the FDA would have denied a warning is to be a question of fact, as Respondents say, then the best available evidence of what the FDA would have done (its own say-so) has to be relevant.

B. Every Other Piece of Evidence Cuts in Merck's Favor as Well

Although the United States' brief is new, its point is hardly novel. Rather, its statements fit neatly with the rest of the record, which already

showed beyond reasonable dispute that the FDA's denial of Merck's proposal was based on more than semantic quibbles. In arguing otherwise, Respondents misread the key document, divorce agency statements from their factual context, and ignore the overwhelming evidence that the agency was not ready to permit any warning until the task force report brought new clarity to the nature of the risk at issue.

Take first the FDA's complete response letter rejecting Merck's proposal. There, the FDA set out its "reasons" for "determin[ing]" it could not grant approval. The first reason? "[Y]our justification for the proposed PRECAUTIONS section language is inadequate." J.A.511.

Respondents insist that the letter "offered only one reason for rejecting" Merck's proposal: that it talked about stress fractures. Resp. Br. 39. Not so. To the extent that the FDA took issue with Merck's references to stress fractures, that was *in addition* to Merck's "inadequate" "justification" for the warning, not an *elaboration* of that inadequacy. After all, FDA provided "*reasons*" for rejecting the PAS—in the plural—not "only one reason." J.A.511.

Next, consider that, at the same time it denied Merck's proposed warning, the FDA also accepted Merck's request to add "low energy femoral shaft *and subtrochanteric* fractures" to the Adverse Reactions sections—with the italicized words differing from Merck's original proposal. J.A.512; *compare* J.A.728. Respondents claim that this shows that the FDA "was willing to approve a warning" but disliked Merck's language. Resp. Br. 41–42. Actually it shows the opposite. The FDA's redline of Merck's

Adverse Reactions proposal—and complete absence of any redlining on Merck's Precautions proposal—confirm that the FDA did not ignore patient safety by rejecting Merck's request for semantic reasons. The disparate treatment of the two proposals flows from the fact that Precautions require a more certain causal association, which the FDA did not believe existed. *See* Merck Br. 9–10.

The agency's conduct before sending the complete response letter drives the point home. A month earlier, an FDA official told Merck to "hold off on the W&P language" so it could "close out these supplements" and then "work with" Merck on a new warning "*if it is warranted.*" J.A.508 (emphasis added). Respondents, omitting the key part of the quote, insist that this document proves the FDA did not "definitive[ly] reject[]" a warning in the complete response letter that followed. Resp. Br. 48. But it did just that: The FDA told Merck it wanted to "*close out*" Merck's PAS, study the issue more, and *then* add a warning "if it is warranted." Respondents have no answer for why the FDA would say such a thing if it already knew enough to accept changes.

Nor can Respondents explain Merck's phone call with the same FDA official who drafted the complete response letter, during which the official told Merck that "[t]he conflicting nature of the literature d[id] not provide a clear path forward, and more time w[ould] be need[ed] for FDA to formulate a formal opinion on the issue of a precaution." J.A.767. Respondents insist that this compelling evidence is "self-serving hearsay." Resp. Br. 47. But they did not object to the record's admission or seek to depose the recordkeeper before the District Court.

The FDA's conduct after the complete response letter also refutes Respondents' story. In March 2010, the FDA told doctors to "continue to follow the recommendations in the [unrevised] label" while it "work[ed] closely with outside experts" "to gather additional information that may provide more insight." J.A.519–20. Respondents fight back against a single line in this document—the FDA cited the lack of a "clear connection" between bisphosphonate use and atypical femoral fractures, but did not deny that there was "reasonable evidence of a causal association," which is the regulatory standard to add a Precaution. Resp. Br. 48–49 n.26. But Respondents do not try to explain why the FDA would have told doctors to *keep prescribing Fosamax as labeled* if it already knew enough to justify a revision.

Finally, whatever doubt might be left at this point vanishes when one considers the events following the task force report. Respondents contend that the FDA's 2010 decision to mandate a warning "confirms that it was possible for Merck to add an adequate warning" earlier. Resp. Br. 48. Again, just the opposite is true. The FDA ultimately chose to mandate a warning *because of* the task force report, which was published only in September 2010. As the Deputy Director of the Office of New Drugs explained, "[b]ased on that report," and particularly its crafting of a provisional case definition, the FDA was "able to better assess some of the cases reported to" it. J.A.488. Indeed, when she was asked "what new data between March and now have you reviewed" to justify a warning, she cited the report,

explaining that it had been "really helpful to [the FDA] in better understanding this." J.A.492–94.

In short, the FDA's refusal to accept (or even to redline) Merck's proposal, along with its insistence that more research was needed before a new warning could be approved, and its ultimate crediting of the task force report for changing its mind, all make it impossible to believe that Merck could have changed its label at any time before September 2010.

C. There Is No Heightened Burden of Proof for Preemption.

The Third Circuit, however, reached a contrary conclusion because it demanded that Merck satisfy a heightened evidentiary burden. Unlike the Third Circuit's speculation about whether a judge or jury should decide what the FDA would have done with a revised warning (which all admit was unnecessary dictum, Resp. Br. 50), the Third Circuit's statements on the burden of proof were essential to its holding: It denied summary judgment solely because, in its view, a reasonable factfinder could find that "the odds of [an] FDA rejection were *less than highly probable*." Pet.App.5a (emphasis added). Respondents' three reasons for imposing such a requirement are unpersuasive.

First, Respondents say that *Levine*'s use of the phrase "clear evidence" is "consistent with a heightened standard of proof." Resp. Br. 56. Maybe so, but it is equally consistent with Merck's reading: that preemption must be based on evidence rather than conjecture. Merck Br. 46; *see, e.g.*, *Block v. Cmty. Nutrition Inst.*, 467 U.S. 340, 350–51 (1984) (using the phrase in this way). And the latter is the

far better reading, because it comports with the general rule that, absent statutory direction, courts do not invent heightened burdens of proof unless fundamental rights are at stake. *See, e.g.*, *Santosky v. Kramer*, 455 U.S. 745, 769–70 (1982) (termination of parental rights); *Addington v. Texas*, 441 U.S. 418, 433 (1979) (involuntary commitment). Respondents do not claim that their mine-run tort suits implicate concerns of that magnitude.

Second, Respondents say a heightened burden is necessary because *Levine* "stretched the bounds of impossibility preemption" by allowing manufacturers to prove preemption even where it is "physically possible" to comply with both state and federal law. Resp. Br. 56. Respondents' premise is wrong: If state law requires a warning that the FDA would prohibit, it is not "physically possible" to issue that warning without violating federal law. And all agree that a manufacturer must make that showing (that is, that the FDA would have prohibited the warning) to prevail on its preemption defense. The question here is by what standard of proof must the manufacturer do so. The difficulty of proving the defense is not a reason to heighten the standard of proof beyond the ordinary preponderance standard that governs all ordinary civil litigation.

Finally, Respondents accuse Merck of conceding that some heightened burden applies, even if it is not quite as high as the clear-and-convincing standard. Resp. Br. 56. That would be irrelevant even if it were true; Respondents feign difficulty imagining "a case that would turn on whether the defense requires proof by clear-and-convincing evidence," Resp. Br. 56–57, but the Third Circuit suggested this

was (in its view) exactly such a case, and that Merck would prevail without the clear-and-convincing standard. Pet.App.62a, 67a.

Anyway, Merck never conceded this. Merck denied that *Levine* imposes a heightened burden, arguing that *Levine*'s "clear evidence" language simply requires courts to base preemption findings on evidence rather than speculation. Merck Br. 46. If the manufacturer produces such evidence, and if it establishes by a preponderance of the evidence that the FDA would have rejected any revised label, then it has carried its burden. Especially given the Supremacy Clause's *non obstante* provision, courts may not distort federal law—for example, by adding a heightened burden—to avoid a conflict with state law. *Mensing*, 564 U.S. at 623 (plurality op.).

III. Respondents' Procedural Complaints Are Meritless and Irrelevant.

Respondents finally argue that the District Court violated due process (or perhaps the Federal Rules of Civil Procedure?) by giving them only 45 days to develop evidence in response to a show-cause order after the bellwether decision in *Glynn*. Resp. Br. 57–58; BIO 29–30 Although this Court need not resolve this complaint—which the Third Circuit never passed upon—the argument is easily rejected.

Respondents had far more than 45 days to gather their evidence. As the District Court explained, they had "been aware of the potential global effects preemption could have on the entire MDL for at least two ... years." Pet.App.124a. Throughout that period—designed to efficiently provide core discovery to all plaintiffs in all cases with respect to common

issues—Respondents "were aware of the exact position that Merck took surrounding preemption," *id.*, and had a full seven months of fact discovery, Pet.App.124a–30a. All of that occurred before *Glynn*'s bellwether trial. Only after that trial, and further briefing on preemption there, did the court order Respondents to show cause, giving them another 45 days to adduce additional evidence. It does not violate due process (or an unspecified rule) to give a party "yet another opportunity ... to address what has *long* been known as the predominant issue in a case." Pet.App.129a–30a.

Nor can Respondents show any real prejudice. They now contend that, with extra time, they would have deposed the Merck employee who took notes during a call with an FDA official. Resp. Br. 58. But Respondents never asked to depose that employee, even though Merck had long pointed to her notes as one piece of evidence in its favor. *See* Dkt. 129, No. 11-cv-05304 (D.N.J.) (*Glynn*). Respondents' remorse over their own procedural missteps is no basis to reverse a grant of summary judgment.

The same goes for Respondents' claim that the "schedule" somehow prevented some of them from arguing that Merck could have issued—and they "would have ... heeded"—a revised warning during the gap between the FDA's rejection of Merck's proposal and the task force's report. Resp. Br. 58 n.32. Manufacturers may amend their labels using the CBE process based only on "newly acquired information." 21 C.F.R. § 314.70(a)(6)(iii). And Respondents never point to any new, material information that emerged after the denial of Merck's proposal (in May 2009) but before the task force

report (in September 2010). Plus, the only evidence Respondents say they would have needed to make this futile point—evidence about "when the warning would have been heeded," Resp. Br. 58 n.32—was exclusively within their own control. It hardly requires more than 45 days to gather *that*.

CONCLUSION

The Court should reverse the judgment below.

December 14, 2018

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No. 17-290

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Petitioner,

v.

DORIS ALBRECHT, ET AL.,
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ARGUMENT

I. The Court's Review Is Unwarranted

The Solicitor General correctly recognizes that this case does not meet the Court's ordinary criteria for certiorari. He concedes there is no "circuit conflict" and acknowledges that allowing percolation in lower courts could "potentially 'simplify the Court's task' by refining the issue for its review." U.S. Br. 23 (alteration omitted). The Solicitor General nonetheless recommends review, while admitting (at 22) that "the question is close." Yet the Solicitor General ignores several unusual aspects of this appeal, which could hinder the Court's resolution of the legal issues presented and which render this a *sui generis* case unlikely to have a broad impact on preemption jurisprudence.

1. This case's unorthodox procedural posture could prevent the Court from reaching the question presented. In the first bellwether trial in this multidistrict litigation, the jury rejected the plaintiff's claim because she had not suffered an atypical femoral fracture. Opp. 10. The district court nonetheless issued an advisory opinion concluding that her claims were preempted. *Id.* At petitioner's urging, the court issued an order to show cause why this advisory opinion should not apply to respondents, plaintiffs in hundreds of separate cases. *Id.* Even though most plaintiffs had not yet begun discovery, the court gave respondents just 45 days to oppose preemption. *Id.* The court's process for disposing of respondents' claims was procedurally improper, as respondents argued below and in their opposition brief (at 29). This Court will confront that threshold issue if it grants certiorari. If it agrees with respondents, that would foreclose review of the merits of the district

court's preemption ruling. The Solicitor General ignores those procedural barriers to review.

2. Given this case's unusual facts, the underdeveloped record would hinder this Court's review. The FDA's Complete Response explaining its rejection of petitioner's proposed warning language focused solely on petitioner's misleading discussion of "stress fractures." It said nothing suggesting inadequate scientific evidence that Fosamax caused atypical femoral fractures. Opp. 18-19. Petitioner therefore "direct[ed] [the Third Circuit's] attention away from [the Complete Response] and instead toward a series of informal FDA communications." App. 47a.

The Solicitor General ignores petitioner's reliance on self-serving hearsay accounts of informal communications with FDA. Yet that reliance counsels against certiorari for two reasons. First, the factual record is underdeveloped. The proceedings below did not permit adequate factual development of the informal FDA communications on which petitioner relied to establish preemption. Most notably, petitioner touted a memorandum by its employee, Charlotte Merritt, recounting a telephone call with FDA, as its "single best piece of evidence." App. 49a n.125. But the abbreviated procedure deprived respondents of the opportunity to depose Merritt or otherwise test the reliability of this double hearsay document.

Second, this case is *sui generis*. Respondents are aware of no other preemption case in which the manufacturer relied on hearsay accounts of informal FDA communications to contradict the plain language of an official regulatory action. The Third Circuit's holding that factual disputes remained for the jury is thus unlikely to have significant influence beyond this case's unusual facts. As the Solicitor General

recognizes (at 23), it is "unclear whether the decision below will influence other courts."

In fact, other circuits have recently resolved preemption appeals without deciding whether the issue is a matter for the judge or jury. *See Cerveny v. Aventis, Inc.*, 855 F.3d 1091, 1103 & n.11 (10th Cir. 2017); *In re Incretin-Based Therapies Prods. Liab. Litig.*, 721 F. App'x 580 (9th Cir. 2017). Either courts of appeals will continue avoiding this issue, making the decision below a one-off with no discernible influence on preemption jurisprudence, or courts of appeals will refine the issue by addressing it. Either way, review here is unwarranted.

3. In recommending review, the Solicitor General notes (at 22-23) that this appeal involves an MDL with hundreds of cases. But this Court's review would have limited impact on those cases.

Regardless of this Court's ruling on the question presented, respondents indisputably will be able on remand to assert failure-to-warn claims premised on petitioner's failure to warn of atypical femoral fractures in the label's Adverse Reactions section. Opp. 30. This Court's review would decide only whether respondents' failure-to-warn claims will also involve the label's Warnings and Precautions section. Opp. 30-31. The Third Circuit also held that numerous non-failure-to-warn claims (*e.g.*, design defect) were not preempted. Opp. 31. The petition did not address those claims, so they are not before the Court. The Solicitor General does not suggest otherwise. U.S. Br. 11 n.9.

If the Court wishes to review a preemption case, it should await a case where the Court's decision would dispose of at least one theory of liability.

II. The Third Circuit's Ruling Was Correct

The Third Circuit properly denied summary judgment because petitioner had not shown, beyond genuine dispute, clear evidence that FDA would have rejected a properly worded warning of atypical femoral fractures. FDA's Complete Response regarding petitioner's proposed warning rejected petitioner's focus on stress fractures but did not conclude that scientific evidence was lacking that Fosamax causes atypical femoral fractures. Opp. 16-19. Petitioner relied on hearsay accounts of informal communications with FDA to support preemption, but the Third Circuit correctly concluded that, at best, those arguments raised factual disputes that could not be resolved on an incomplete record. Opp. 20-21. The Solicitor General's attacks on the decision below rest on legal errors and mischaracterizations of the record.

1. The Solicitor General argues that this Court's decision in *Wyeth v. Levine*, 555 U.S. 555 (2009), requiring a brand-name drug manufacturer to show "clear evidence that the FDA would not have approved a change to [a drug's] label," *id.* at 571, is always inapplicable when FDA has made a labeling decision. U.S. Br. 16-19. That argument is waived. Petitioner conceded below that the "clear evidence" standard applied, Pet'r C.A. Br. 31, and argued that it satisfied that standard, *id.* at 40-53. Moreover, no lower court has adopted the Solicitor General's limitation on *Levine*. Opp. 13-15. The Court should not grant certiorari to consider an argument that was waived below and that has never been adopted by any court.

In any event, the Solicitor General misunderstands this Court's precedents and state tort law. FDA rejection of one specific proposed warning does not necessarily establish preemption. That is because a

manufacturer must "show, by 'clear evidence,' that the FDA would have rescinded *any change* in the label and thereby demonstrate that it would in fact have been impossible to do under federal law what state law required." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 624 n.8 (2011) (quoting *Levine*, 555 U.S. at 571) (emphasis added). To establish liability for failure to warn under state law, a plaintiff must show that the existing "warning was insufficient," but "[t]here may . . . be[] any number of ways" for a manufacturer to meet its duty to warn. *Levine*, 555 U.S. at 565. As long as there is an adequate warning under state law that FDA would not have rescinded, compliance with state and federal law is possible.

FDA's rejection of proposed warning language may be part of a manufacturer's showing of clear evidence of impossibility, but it is not alone sufficient, nor does it excuse the manufacturer from its burden of proof. Additional factors may show that an adequate warning was possible. For example, the rejected warning might differ significantly from a warning plaintiffs contend would be adequate. *See Reckis v. Johnson & Johnson*, 28 N.E.3d 445, 459 (Mass. 2015), *cert. denied*, 136 S. Ct. 896 (2016). FDA might not have had all relevant data supporting the warning. *See Incretin-Based Therapies*, 721 F. App'x at 583-84. For injuries occurring after FDA's labeling decision, information emerging after that decision might have supported a label change. *See Hunt v. McNeil Consumer Healthcare*, 6 F. Supp. 3d 694, 701 (E.D. La. 2014). Thus, in cases involving an FDA labeling decision, courts apply the clear-evidence standard based on careful analysis of the decision and other relevant context. *See, e.g., Cerveny*, 855 F.3d at 1098-1106; *Reckis*, 28 N.E.3d at 457-60.

The Solicitor General's contention that rejection of one warning should preempt claims that petitioner should have added a different warning is emblematic of overbroad preemption theories based on "interpretation of broad federal policy objectives, legislative history, or generalized notions of congressional purposes that are not contained within the text of federal law." *Levine*, 555 U.S. at 587 (Thomas, J., concurring in the judgment).

2. The Solicitor General mischaracterizes the record. To support his preemption theory, the Solicitor General portrays (at 19-21) the Complete Response as a determination that the data were insufficient for *any* warning of atypical femoral fractures. That argument differs starkly from petitioner's theory below. Petitioner focused almost exclusively on informal communications with FDA, barely mentioning the Complete Response. Pet'r C.A. Br. 40-53. As the Third Circuit noted, petitioner "direct[ed] our attention away from [the Complete Response] and instead toward a series of informal FDA communications," App. 47a, contending that preemption was established based on communications "not disclosed in the [Complete Response]," App. 53a n.135. The Court should not grant certiorari to consider a theory not presented to the Third Circuit.

In any event, petitioner had good reason to run away from the Complete Response rather than to embrace it as the Solicitor General does: the Solicitor General's characterization of the Complete Response cannot be squared with the letter's text. The Complete Response says that FDA rejected petitioner's proposed warning because it focused on *stress fractures*, not because there was insufficient evidence that Fosamax caused *atypical femoral fractures*, the injury alleged by respondents. The Complete Response read in pertinent part:

> While the Division agrees that atypical and subtrochanteric fractures should be added to the **ADVERSE REACTIONS, Post-Marketing Experience** subsections of the FOSAMAX Tablets and Oral Solution and FOSAMAX Plus D Tablets labels, your justification for the proposed **PRECAUTIONS** section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting.

C.A.App. 1500-01.

The first sentence says that petitioner's "justification" for its proposed "language" was "inadequate." The next two sentences explain why. Specifically, the "literature" did not support "[i]dentification of 'stress fractures'" in relation to atypical femoral fractures. Furthermore, "[d]iscussion of the risk factors for stress fractures" was "not adequately supported" by available literature and data.

The Complete Response shows that FDA rejected petitioner's specific language because its focus on stress fractures was not justified by atypical femoral fractures data. The Solicitor General highlights FDA's references to the literature and adverse event data to argue (at 21) that "FDA's decision . . . was based on the lack of adequate data to support a warning." But FDA said the data were inadequate to support a warning *about stress fractures*. Indeed, petitioner understood the Complete Response contemporaneously as a determination that "FDA wouldn't[] let us mention stress fractures," C.A.App. 1506, not

(as the Solicitor General contends *post hoc*) that FDA would not let petitioner warn of atypical femoral fractures.

Other evidence contradicts its position that FDA rejected *any* atypical femoral fracture warning for insufficient scientific evidence. Shortly before sending the Complete Response, FDA wrote that it wanted to "work with . . . [petitioner] to decide on language for a [Warnings and Precautions] atypical fracture language, if it is warranted." C.A.App. 1498. That message indicates that, although FDA rejected petitioner's stress fracture language, it was open to approving more appropriate warning language. That outreach would have made no sense if FDA had definitively rejected any warning. The Solicitor General ignores that document.

The Solicitor General erroneously relies (at 22) on the fact that FDA did not *require* a label change under 21 U.S.C. § 355(*o*)(4) until October 2010. The Court explained in *Levine* that Section 355(*o*)(4) did not "require[] the FDA to preapprove all changes to drug labels" and "adopted a rule of construction . . . that manufacturers remain responsible for updating their labels." 555 U.S. at 567. Although FDA repeatedly invited petitioner to "work with" it on alternative language and "resubmit" a labeling supplement, C.A.App. 1498, 1501, petitioner rebuffed those entreaties and did nothing.[1] The Third Circuit correctly

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[1] The Solicitor General notes (at 5-6, 21) FDA's practice of communicating "easily correctable deficiencies" to applicants. But the deficiencies of petitioner's proposal were not easily correctible, as *every* sentence after the first focused on stress fractures. C.A.App. 1371. The warning that FDA ultimately approved, C.A.App. 1070-71, reveals that petitioner would have needed to rewrite its proposal completely to render it adequate.

concluded that "the ball was back in [petitioner's] court to submit a revised, corrected proposal," and the record supported the inference that "it was [petitioner's] failure to re-submit a revised CBE or PAS without stress-fracture language, rather than the FDA's supposedly intransigent stance on the science, that prevented the FDA from approving a label change." App. 67a.[2]

3. The Solicitor General advocates (at 12) granting certiorari to decide whether conflict preemption under *Levine* is a matter for the judge or jury. In this case, however, summary judgment would be inappropriate under either approach because the underdeveloped record left unresolved factual disputes. That deficiency resulted from the district court's extraordinary procedural decision to decide preemption on an order to show cause rather than the more typical custom of cross-motions for summary judgment based on a fully developed record.

Respondents argued below, and still believe, that the Complete Response warrants rejection of petitioner's preemption defense as a matter of law. FDA was required to "describe all of the specific deficiencies that the agency has identified," 21 C.F.R. § 314.110(a)(1),[3] but FDA did not identify deficiencies

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[2] Even if the Complete Response reflected FDA's "determination that the data was *then insufficient* to justify . . . a warning," U.S. Br. 19 (emphasis added), that would not dispose of many respondents' claims. More than 200 respondents were injured after the May 2009 Complete Response. *See* Dist. Ct. Dkt. 2857-2. The Complete Response could not possibly prove FDA would have rejected a warning at a later date, as new scientific evidence emerged.

[3] As the Solicitor General notes (at 21), if FDA determines "that the data submitted are inadequate to support approval" of an application, FDA can issue a complete response letter

in the evidence that Fosamax causes atypical femoral fractures. Petitioner sought to contradict the official regulatory record by suggesting that FDA "gave additional reasons for the rejection, not disclosed in the [Complete Response] letter." App. 53a n.135. Petitioner's "single best piece of evidence" was Merritt's memorandum recounting a telephone conversation with FDA. App. 49a n.125; C.A.App. 1970-71. The Third Circuit recognized that deciding whether this document supported preemption required subsidiary factual determinations, including a "credibility determination" of Merritt and "determin[ing] the veracity and accuracy of the notes." App. 49a n.125. But the district court's abbreviated procedure denied respondents the opportunity to conduct discovery (*e.g.*, deposing Merritt) necessary to test petitioner's evidence.

Petitioner's theory below was that hearsay accounts of informal FDA communications established preemption; that contention raises factual disputes that preclude summary judgment regardless of whether the judge or jury is the factfinder. The Solicitor General's novel theory, that the Complete Response itself establishes preemption as a matter of law, is waived. Accordingly, the Solicitor General is incorrect (at 12) that this case "cleanly presents" the question whether preemption is decided by a judge or jury. Affirmance would be required regardless of the answer to that question.

"without first conducting required inspections and/or reviewing proposed product labeling." 21 C.F.R. § 314.110(a)(3). But this provision applies generally to applications "for drug products," not just labeling changes. 73 Fed. Reg. 39,588, 39,592 (July 10, 2008). FDA could not decide on an application seeking only a label change without reviewing the proposed labeling.

4. The Third Circuit correctly held that, when a preemption question under *Levine* raises factual disputes that cannot be resolved on summary judgment, those disputes should be submitted to the jury. Determining the applicable legal standard is a legal question. Yet resolving a preemption defense in a particular case may require finding facts and drawing inferences regarding FDA's actions. This "application-of-legal-standard-to-fact sort of question" is "commonly called a 'mixed question of law and fact.'" *United States v. Gaudin*, 515 U.S. 506, 512 (1995) (citation omitted). Such mixed questions "ha[ve] typically been resolved by juries." *Id.* In *Boyle v. United Technologies Corp.*, 487 U.S. 500 (1988), the Court held that "whether the facts establish the conditions for" a preemption defense "is a question for the jury." *Id.* at 514. The Solicitor General does not mention *Boyle* or provide any basis to distinguish it.

The Solicitor General's position that preemption is a pure legal issue stems from its incorrect view that a written FDA decision rejecting specific proposed warning language alone can establish preemption, regardless of the topics discussed in the proposed labeling or the risks faced by patients. The Solicitor General therefore analogizes (at 14-15) to *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996), which held that patent construction is a legal matter for the judge. However, this analogy breaks down because "the immediate 'legal' effect of the [Complete Response] letter . . . was simply to reject [petitioner's] proposed warning. That limited determination informs but does not answer the larger question of whether the FDA would have approved a differently-worded warning." App. 53a n.135.

That larger question may involve factual disputes appropriate for a jury. This case presents a perfect example. Petitioner's reliance on Merritt's memorandum raises "precisely the types of personal evaluations and weight-of-the-evidence assessments that [courts] commit to jurors in the first instance." App. 49a n.125.

To be sure, many preemption questions turn on undisputed facts regarding FDA's official regulatory actions. Courts can resolve such cases on summary judgment. *See, e.g., Cerveny*, 855 F.3d at 1099-1106. But in unusual cases like this one, the manufacturer's preemption arguments raise factual disputes that cannot be resolved in its favor on summary judgment.

CONCLUSION

The petition for a writ of certiorari should be denied.

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The United States agrees that the Third Circuit's approach to drug preemption is misguided, and that this Court's immediate review is warranted due to the "importan[ce]" and "practical implications" of the legal question. U.S. Br. 23. In this sensitive area of law, the Court has granted certiorari even when the United States has recommended *against* it. *See, e.g.*, *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011). The same result should follow *a fortiori* here, despite the dust that Respondents now attempt to kick up.

1. Respondents begin by rehashing supposed "vehicle" problems that Merck has already rebutted. Those arguments have not improved with age or repetition. They amount to nothing, which is why the United States "ignore[d]" them. Supp. Br. 2.

First, there is no reason why this Court would have to "confront" the purportedly "threshold" issue of the district court's (perfectly proper) show-cause procedure. Supp. Br. 1. The Third Circuit bypassed that issue entirely, and Respondents do not claim it poses any jurisdictional obstacle. At most, it could therefore be an issue to address on remand after this Court vacates the Court of Appeals' erroneous legal ruling on the merits. *See* Merck Reply 10.

Second, the record is hardly "under-developed." Supp. Br. 2. The trial court gave Respondents ample opportunity to develop evidence in opposition to the preemption defense (*see* Pet.App.136a), and the only "missing" evidence that Respondents identify is an unrequested deposition of a Merck employee about her notes from a single phone call with FDA. The rest of the record, however, makes clear that Respondents' claims are preempted as a matter of law, even without those notes. *See* Merck Reply 5, 11; U.S. Br. 19–22.

Third, Respondents assert that, because this case will not resolve *all* claims against Merck, it is not worth resolving *any* of them. Supp. Br. 3. This Court's decision would knock out the most important theories in these myriad cases: those alleging (either directly or derivatively) that Merck should have revised the Warnings & Precautions section of the label prior to October 2010. Just as importantly, this Court's ruling would clarify a confused area of law that governs a high volume of cases with substantial policy implications. *See* U.S. Br. 23; Merck Reply 10.

2. In addition to the re-warmed arguments from their brief in opposition, Respondents now raise two new "vehicle" problems—Merck's alleged "waiver" of arguments advanced by the United States. There was no waiver. Respondents simply mischaracterize both the United States' position and Merck's.

Respondents contend that Merck never pressed the United States' theory that *Wyeth v. Levine*, 555 U.S. 555 (2009), is "inapplicable when FDA has made a labeling decision." Supp. Br. 4. That is semantics. The United States correctly explained that *Levine* "did not resolve how to determine the meaning and effect of an actual FDA labeling-supplement decision," as no warning had been proposed in that case. U.S. Br. 17. When FDA *has* acted on a proposal, the question is "how to interpret FDA's actual labeling decision." U.S. Br. 19. If that decision reflects a science-based rejection of a warning—as here—then contrary state-law claims are preempted. U.S. Br. 19; *see also* Merck C.A. Br. 40–53. Whether FDA's *actual* decision is characterized as "clear evidence" of what FDA *would have done*, thereby satisfying *Levine*, or instead as an *exception* to *Levine*, makes no substantive difference.

Respondents also suggest that, while the United States relies heavily on FDA's Complete Response Letter to support its interpretation of FDA's actions, Merck "barely mention[ed]" that letter below. Supp. Br. 6. Not true. Merck has consistently argued that FDA's formal response reflected the agency's science-based ground for rejecting its request. *See, e.g.*, Merck C.A. Br. 49 (citing FDA's "formal response" to show what the agency "clearly understood"); Merck Reply 5–6. To be sure, Merck has also highlighted other evidence to corroborate that interpretation of FDA's letter. But the United States equally accepts that construction of the Complete Response Letter may turn on "the surrounding regulatory framework and related FDA actions." U.S. Br. 15; *see also id.* (acknowledging that "extrinsic evidence may sometimes be relevant to determine the meaning and effect of FDA's agency action"). Again, Respondents are imagining a divergence that does not exist.

3. Last, Respondents continue to insist that the Third Circuit reached the right result, because (they say) FDA rejected Merck's proposed warning based on disapproval of Merck's terminology, "not because there was insufficient evidence" that Fosamax posed the safety risk. Supp. Br. 6. That "fact," according to Respondents, precludes Merck from prevailing on its preemption defense, or at least requires that a *jury* resolve it as a question of *fact*. Supp. Br. 6–10.

That attempt to duck the question presented was unpersuasive and at odds with the record even before the United States filed its brief (Merck Reply 3–6); it is absolutely untenable in light of what FDA has now represented about its regulatory practices in general and its decisions about Fosamax in particular.

As the United States' brief explains, regulations compel FDA to cooperate with manufacturers when there is a scientific basis for a warning; the agency does not reject warnings on "editorial" grounds. U.S. Br. 5–6. To the contrary, if FDA comes to believe that new safety information justifies a label warning, the agency is "required" by statute to notify the drug manufacturer and "engage in expedited discussions to revise the labeling." U.S. Br. 22 (citing 21 U.S.C. § 355(o)(4)). Consistent with that legal background, FDA's rejection of Merck's proposed warning "was based on the agency's determination that the data was then insufficient to justify such a warning." U.S. Br. 19. There is "[n]o sound basis" to conclude that, as Respondents insist, FDA rejected the proposal "because of [Merck's] proposed text." U.S. Br. 21.*

With FDA having now cleared away any doubt regarding the regulatory scheme and its approach to proposed warnings, nothing stands in the way of resolving the question presented: When a drug manufacturer tells FDA everything it knows about a safety risk and proposes a warning, but FDA *refuses* to approve the warning, can a lay jury nonetheless hold the manufacturer liable for its failure to warn, based on the *speculation* that the agency *might* have approved some alternatively worded warning?

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* Respondents also note that an FDA rejection might not suffice to establish preemption if FDA did not have "all relevant data" or if new data "emerg[ed] after [its] decision." Supp Br. 5. True, but this case involves neither circumstance. U.S. Br. 19 n.10. Respondents never identify any missing or new data.

* * *

Lower courts and regulated parties remain confused and uncertain about the meaning and scope of this Court's decision in *Levine*. At a minimum, this case will determine the approach to preemption in the particular context of an FDA decision rejecting a proposed warning. As the United States explains, that is a significant question in its own right, *see* U.S. Br. 22, and one that arises regularly, *see, e.g.*, *Cerveny v. Aventis, Inc.*, 855 F.3d 1091 (10th Cir. 2017); *Reckis v. Johnson & Johnson*, 28 N.E.3d 445 (Mass. 2015).

More generally, and as the United States further reaffirms, *see* U.S. Br. 23, this case should also shed light on broader questions, such as whether *Levine* adopted a "clear and convincing" evidence standard and whether a judge or a lay jury should decide whether a plaintiff's claims are preempted. Given the importance of this area of law to public safety, the pharmaceutical industry, and FDA's mission—as now confirmed by the United States—this Court should grant review to provide the requisite guidance.

CONCLUSION

The petition should be granted.

JUNE 7, 2018

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No. 17-290

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QUESTION PRESENTED

Whether a state-law failure-to-warn claim alleging the insufficiency of brand-name drug labeling is preempted by the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.*, when the Food and Drug Administration, after the drug manufacturer provided it with the relevant scientific data, rejected the manufacturer's application to modify its labeling to warn about the risk underlying the tort claim.

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BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING PETITIONER

INTEREST OF THE UNITED STATES

This case concerns the circumstances under which a decision of the Food and Drug Administration (FDA) rejecting proposed changes to the labeling of a brand-name drug preempts state-law tort claims that allege that the drug manufacturer failed to provide adequate warnings on its labeling. At the Court's invitation, the United States filed a brief as amicus curiae at the petition stage of this case.

STATEMENT

1. This case involves a series of tort claims alleging that petitioner's labeling for its Fosamax drug products insufficiently warned of the drugs' risks. Petitioner has argued, among other things, that many of the failure-to-warn claims are preempted because, in 2009, FDA rejected its attempt to strengthen relevant warnings on

that labeling. The regulatory scheme for drug labeling establishes the framework for that defense.

a. Congress has charged FDA with ensuring that each "drug is safe for use under the conditions prescribed, recommended, or suggested" in its "labeling." 21 U.S.C. 355(d); cf. 21 U.S.C. 321(m) (defining "labeling"); 21 U.S.C. 352(f) (misbranding). FDA regulations govern the content and format of prescription-drug labeling. See, *e.g.*, 21 C.F.R. 201.56, 201.57; see 21 C.F.R. 201.100(c). Those regulations are intended to organize labeling information to more effectively communicate to healthcare professionals the "information necessary for the safe and effective use of prescription drugs." 71 Fed. Reg. 3922, 3928 (Jan. 24, 2006). Two separate labeling sections now generally required on prescription-drug labeling are relevant here: the Warnings and Precautions section and the Adverse Reactions section. See 21 C.F.R. 201.57(c)(6) and (7).[1]

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[1] The specific requirements for labeling content and format discussed in the text generally apply to prescription drugs subject to a new drug application (NDA) or efficacy supplement approved on or after June 30, 2001. 21 C.F.R. 201.56(b)(1). The specific labeling requirements for older drug products differ in certain respects. See 21 C.F.R. 201.56(e), 201.80.

This case involves the labeling of three FDA-approved Fosamax products: Fosamax tablets (NDA 20560, approved 1995); Fosamax oral solution (NDA 21575, approved 2003); and Fosamax Plus D tablets (NDA 21762; approved 2005). See J.A. 510-511; see also FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations* 3-12, 6-14 (38th ed. 2018) (listing Fosamax products). Although the newer labeling requirements discussed in this brief did not apply to all of those products at the time relevant here, no party has suggested that the differences between the two sets of labeling requirements are relevant to this case. The government agrees. This brief therefore follows the path taken by the court of appeals,

The Warnings and Precautions section must identify "clinically significant adverse reactions" and certain other safety hazards where "reasonable evidence of a causal association" between the drug and such hazards exists. 21 C.F.R. 201.57(c)(6); see 73 Fed. Reg. 49,603, 49,604 (Aug. 22, 2008) (stating that a "'preponderance' of evidence" is not required). FDA adopted that causal standard in part to "prevent overwarning" of potential risks, which, if included in the Warnings and Precautions section, could dilute other "more important warnings" or "deter appropriate use" of the drug. 73 Fed. Reg. at 49,605-49,606. FDA thus reserves this section for only a "discrete set" of hazards serious enough to affect prescribing decisions. FDA, *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* 3 (Oct. 2011), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf.[2]

The Adverse Reactions section, by contrast, describes "the overall adverse reaction profile of the drug." 21 C.F.R. 201.57(c)(7). The causal threshold for including an adverse reaction in this section is lower than that for the Warnings and Precautions section: An adverse reaction must be listed if "some basis" exists

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which based its decision on the newer labeling requirements in Section 201.57(c) without discussing Section 201.80. See Pet. App. 7a-9a & nn.6, 9-10, 16, 51a n.130, 63a-64a nn.154, 156.

[2] The 2011 guidance describes FDA's interpretation of its 2006 labeling regulations. FDA has informed this Office that the 2011 guidance accurately reflects how FDA treated the Warnings and Precautions section during the period relevant here.

"to believe there is a causal relationship between the drug and the occurrence of the adverse event." *Ibid.*

b. A brand-name drug "manufacturer bears responsibility for the content of its label[ing] at all times." *Wyeth* v. *Levine*, 555 U.S. 555, 570-571 (2009); see 21 U.S.C. 355(*o*)(4)(I). When new information becomes available about a new risk or a new aspect of a known risk that causes existing labeling to become inadequate, the manufacturer is responsible for pursuing a revision to its labeling. See 21 C.F.R. 201.57(c)(6)(i) (stating that updated warning must be added "as soon as" sufficient causal evidence of a clinically significant hazard exists); 21 C.F.R. 201.57(c)(7)(ii)(B) (requiring list of adverse reactions identified in postmarketing experience); cf. 21 C.F.R. 201.56(a)(2) (requiring updated labeling "when new information becomes available that causes the labeling to become inaccurate, false, or misleading").[3]

i. After FDA has approved a new drug application (NDA) for a drug, 21 U.S.C. 355(b)(1) and (d), two mechanisms exist for changing a brand-name prescription drug's labeling, both of which require that the manufacturer file a supplemental NDA for FDA approval. First, the sponsor may submit a Changes Being Effected (CBE) supplement for certain labeling changes, which allows the manufacturer immediately to implement its proposed labeling changes upon FDA's receipt of the supplement. 21 C.F.R. 314.70(c)(6) and (iii); see *Wyeth*, 555 U.S. at 571, 573. A CBE supplement may be submitted, for instance, to add or strengthen a warning,

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[3] Because a generic drug's labeling generally must track that of its reference listed drug, generic-drug manufacturers cannot independently change such labeling. See, *e.g.*, *Mutual Pharm. Co.* v. *Bartlett*, 570 U.S. 472, 486, 488 (2013); *PLIVA, Inc.* v. *Mensing*, 564 U.S. 604, 613-615, 618 (2011).

precaution, or adverse reaction to reflect "newly acquired information" if "the evidence of a causal association satisfies the [relevant] standard for inclusion in the labeling." 21 C.F.R. 314.70(c)(6)(iii)(A); see 21 C.F.R. 314.3(b) (defining "[n]ewly acquired information"). If FDA later disapproves the supplement, however, it may order the manufacturer to cease distributing the drug with the labeling changes. 21 C.F.R. 314.70(c)(7).

Second, the sponsor may submit a Prior Approval Supplement (PAS) to propose labeling changes. 21 C.F.R. 314.70(b) and (2)(v). Under that procedure, FDA approval is required before the changes are made. 21 C.F.R. 314.70(b)(3). A PAS "must be submitted" for certain types of changes that "include, but are not limited to," certain labeling changes other than those described in Section 314.70(c)(6)(iii) for CBE supplements. 21 C.F.R. 314.70(b)(1), (2), and (v)(A). Historically, FDA has also accepted PAS applications instead of CBE supplements, as occurred in this case, particularly where significant questions exist on whether to revise or how to modify existing drug labeling.[4]

ii. "All procedures and actions that apply to an application" submitted to FDA generally apply "to supplements." 21 C.F.R. 314.71(b) and (c). FDA has accordingly confirmed to this Office that it follows many of the general principles applicable to its review of an NDA when undertaking the more limited task of reviewing supplements that propose safety-related labeling changes. More specifically, FDA communicates with the applicant about "scientific, medical, and procedural issues that

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[4] Cf. FDA, *Guidance for Industry: Safety Labeling Changes—Implementation of Section 505(o)(4) of the FD&C Act* 7 (July 2013), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf.

arise" in the course of its review. 21 C.F.R. 314.102(a). The "[d]evelopment of final labeling" generally is then "an iterative process between the applicant and FDA" involving a series of communications.[5] If FDA reviewers identify "easily correctable deficiencies" in a supplement, they will "make every reasonable effort to communicate [them] promptly to applicants." 21 C.F.R. 314.102(b). And if only "editorial or similar minor deficiencies in the [proposed] labeling" exist, FDA may approve the supplement on the condition that the applicant makes appropriate corrections and submits a copy of the final labeling before marketing the drug with that labeling. 21 C.F.R. 314.105(b).

FDA will reject a supplement, however, if the proposed labeling change is false or misleading or if it does "not comply with the requirements for labels and labeling in [21 C.F.R. P]art 201." 21 C.F.R. 314.125(b)(6) and (8). In such circumstances, FDA will send the applicant a "complete response letter." 21 C.F.R. 314.110(a). A complete response letter reflects FDA's "complete review of the data submitted" and "will describe all of the specific deficiencies that the agency has identified." 21 C.F.R. 314.110(a)(1) and (2).

2. a. Petitioner is the manufacturer of Fosamax, a brand-name drug that FDA approved in tablet form in

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[5] See Center for Drug Evaluation & Research, FDA, *CDER 21st Century Review Process: Desk Reference Guide* 37 (2014), https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf; see also FDA, *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products* 21 (Apr. 2005), https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079748.pdf (addressing "communication between the FDA and applicants" during "labeling discussions").

1995 for the treatment of osteoporosis in postmenopausal women. Pet. App. 5a, 12a; see p. 2 n.1, *supra*. Evidence later began to emerge suggesting a connection between Fosamax and an increased risk of an unusual type of thigh-bone fracture known as an "atypical femoral fracture[]," which occurs with no or minimal external trauma and results in a complete fracture of the femur. Pet. App. 6a, 13a-14a. Petitioner kept FDA informed of those studies. *Id.* at 13a.

In June 2008, FDA informed petitioner that it was aware of reports regarding the occurrence of atypical femoral fractures in patients using bisphosphonates like Fosamax. C.A. App. A1935-A1936. FDA stated that it was "concerned about this developing safety signal" and asked petitioner to submit any information it had on the issue. *Ibid.* Petitioner promptly complied. Pet. App. 14a.

b. In September 2008, petitioner submitted three Prior Approval Supplements for its three Fosamax products that proposed changing the relevant labeling to address atypical femoral fractures in two respects. Pet. App. 14a-15a; see p. 2 n.1, *supra*.[6]

First, in the Adverse Reactions section (J.A. 715-729), petitioner proposed adding a reference to "low-energy femoral shaft fracture." J.A. 728; see Pet. App. 16a. Petitioner also proposed including a parenthetical cross-reference to direct readers to a discussion of "Low-Energy Femoral Shaft Fracture" proposed for the Warnings and Precautions section. J.A. 728 ("(see

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[6] Relevant portions of one of the PAS applications are available at J.A. 669-761; see C.A. App. A2697-A2928 (reproducing additional portions). FDA has confirmed to this Office that petitioner proposed the same relevant labeling language for each of its three Fosamax products.

PRECAUTIONS, Low-Energy Femoral Shaft Fracture)") (emphasis omitted).

Second, in the Warnings and Precautions section (J.A. 703-715), petitioner proposed adding a new subsection with an identical title: "Low-Energy Femoral Shaft Fracture." J.A. 707 (emphasis omitted); see Pet. App. 15a. That subsection stated that "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients." J.A. 707. The proposed warning added that "[s]ome" of those fractures were "stress fractures (also known as insufficiency fractures)," and the remainder of petitioner's proposed text repeatedly referenced stress fractures. *Ibid.*[7]

Petitioner supported its applications with evidence regarding femoral fractures in Fosamax users. Pet. App. 16a; see, *e.g.*, J.A. 745-761; C.A. App. A2748-A2928. The applications stated, as relevant, that petitioner's use of the term "stress fracture" in connection with reports of "low-energy subtrochanteric/mid femoral shaft fractures" referred to an "insufficiency fracture" that occurs with no "identifiable external traumatic event." J.A. 746, 748; see J.A. 748-749, 751. The treatment data in the applications indicated that 91% of the fractures resulted in surgical intervention and the other 9% involved patients who sustained only "incomplete stress fractures." J.A. 753.

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[7] An "insufficiency f[racture]"—which can be associated with "osteoporosis"—is "a stress fracture that occurs during normal stress on a bone of abnormally decreased density"; it is thus different from the type of "stress f[racture]" experienced by athletes (a fatigue fracture) "caused by unusual or repeated stress on a bone." *Dorland's Illustrated Medical Dictionary* 710-711 (29th ed. 2000).

In May 2009, FDA issued a Complete Response Letter (J.A. 510-513) informing petitioner that FDA could not "approve the[] applications in their present form." J.A. 511; see Pet. App. 18a. FDA stated that it "agree[d] that atypical and subtrochanteric fractures should be added" to the Adverse Reactions labeling section. J.A. 511. FDA therefore recommended that petitioner modify its proposed text (J.A. 728) for that section to read "low energy femoral shaft and subtrochanteric fractures." J.A. 512. With respect to petitioner's Warnings and Precautions proposal, however, FDA determined that the "justification for the proposed [Warnings and Precautions] section language is inadequate." J.A. 511. The letter also stated that "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature" and that "[d]iscussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and postmarketing adverse event reporting." J.A. 511-512.

In June 2009, petitioner updated the Adverse Reactions section of its Fosamax labeling (J.A. 253, 267-274) using FDA's recommended text. J.A. 274; see J.A. 279. Petitioner then withdrew its three pending PASs, J.A. 654-655, and submitted new CBE supplements for that labeling change as the "quickest route to upd[illegible]e" its labeling, J.A. 657-658. FDA later approved these CBE supplements.[8]

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[8] See FDA, *Supplement Approval* 1-2 (Mar. 1, 2010), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/020560s051s055s057,021575s012s016s018ltr.pdf (NDA 20560/S-057 and 21575/S-018); FDA, *Supplement Approval* 1-2 (Mar. 1, 2010), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/021762s005s009sS010ltr.pdf (NDA 21762/S-010).

c. Nearly a year after its Complete Response Letter, and after reviewing additional data submitted by petitioner and other manufacturers, FDA issued a Safety Announcement in March 2010 (J.A. 519-522) stating that "FDA's review of these data did not show an increase in [a] risk [of atypical subtrochanteric femur fractures] in women using [bisphosphonates]," but that FDA was working with an outside expert task force to "gather additional information." J.A. 519-520 (stating that the data "ha[d] not shown a clear connection between bisphosphonate use and [that] risk"); see Pet. App. 19a.

On September 14, 2010, the task force completed its report, which identified an apparent association between long-term bisphosphonate use and certain atypical femoral fractures. Pet. App. 20a; see J.A. 523.

d. On October 13, 2010, after studying the report, FDA exercised its authority under 21 U.S.C. 355(*o*)(4) to initiate safety-based changes to Fosamax's labeling. See J.A. 526-527, 546 (FDA letter dated Oct. 13, 2010). Under Section 355(*o*)(4), the Secretary of Health and Human Services, acting through FDA, "shall promptly notify" a brand-name drug manufacturer as the "responsible person" for a drug "[i]f the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug." 21 U.S.C. 355(*o*)(4)(A); see 21 U.S.C. 355(*o*)(2)(A)(ii) (defining "responsible person"). Within 30 days, the manufacturer then must either submit a supplemental application to change the labeling or notify the Secretary that (and explain why) it believes that no change is warranted. 21 U.S.C. 355(*o*)(4)(B). The Secretary must "promptly review and act upon such supplement" and,

if the Secretary disagrees with the manufacturer's labeling proposal or disagrees with the manufacturer's view that no changes are warranted, the Secretary "shall initiate discussions" to reach agreement within 30 days regarding a labeling change. 21 U.S.C. 355(*o*)(4)(C) and (D). The Secretary may thereafter "issue an order directing" the manufacturer "to make such a labeling change as the Secretary deems appropriate to address the new safety information." 21 U.S.C. 355(*o*)(4)(E).

FDA announced its decision to the public by explaining that it was requiring bisphosphonate manufacturers to modify their labeling to include information regarding the risk of such fractures in, among other places, the Warnings and Precautions section. J.A. 246, 249. In a briefing to reporters, FDA's Deputy Director for the Office of New Drugs explained that the data that FDA had previously reviewed was insufficient to allow the agency to "tease out the association between [bisphosphonates] and these rare atypical fractures," but that the task force's September 2010 report had helped FDA "understand the[] fractures" better, "provide[d] more information that more closely associate[d] the[] atypical fractures with long-term bisphosphonate use," and persuaded FDA that such fractures were "more closely related to these drugs * * * than [FDA] previously had evidence for." J.A. 488-489, 493-494; see J.A. 486.

FDA's October 2010 letter invoking Section 355(*o*)(4) likewise notified petitioner that FDA "ha[d] become aware of a possible increased risk of atypical subtrochanteric and diaphyseal femoral fractures in patients taking bisphosphonates, including Fosamax," and that FDA now believed that new safety information about that risk should be included in Fosamax's labeling, in-

cluding changes to the Warnings and Precautions section. J.A. 527, 528-529. In response, petitioner proposed a labeling change that utilized the term "stress fractures." Pet. App. 22a. FDA thereafter struck those references from petitioner's proposal in the course of approving the labeling change because, an FDA employee explained, the term would suggest to most practitioners "a minor fracture" that "would contradict the seriousness of the atypical femoral fractures" at issue. J.A. 566, 606-607; see Pet. App. 22a-23a; cf. J.A. 547, 549-628 (redline showing FDA edits to petitioner's proposed labeling).

3. Over 1000 plaintiffs subsequently filed separate state-law tort actions against petitioner, alleging that they had sustained atypical femoral fractures caused by taking Fosamax. Pet. App. 4a, 23a. Although plaintiffs asserted an array of tort theories, they generally alleged that petitioner had failed to provide adequate warnings on its Fosamax labeling. *Id.* at 4a, 24a. The cases were consolidated for pretrial proceedings as a multidistrict litigation (MDL). *Id.* at 23a.

One bellwether case within the MDL was selected for trial on its failure-to-warn claim. Pet. App. 24a-25a & n.64. Petitioner moved for summary judgment on preemption grounds, but the district court did not immediately rule on the motion. *Id.* at 163a. After a jury rendered a verdict for petitioner on case-specific grounds, the court rendered a post-trial decision holding that the bellwether plaintiffs' failure-to-warn claim was preempted. *Id.* at 25a-26a, 153a-174a.

The district court subsequently extended that preemption holding to the other MDL cases in which the plaintiff was injured before September 14, 2010—the

date of the expert task force report—and granted judgment to petitioner in those cases. Pet. App. 152a; see *id.* at 113a-152a.

4. The court of appeals vacated and remanded. Pet. App. 1a-74a.

The court of appeals concluded that its impossibility-preemption analysis was controlled by this Court's decision in *Wyeth* v. *Levine*, *supra*, which the court viewed as teaching that a drug-focused failure-to-warn claim is preempted "where there is 'clear evidence that the FDA would not have approved a change' to the label," Pet. App. 32a-33a (quoting *Wyeth*, 555 U.S. at 571). See *id.* at 28a-55a. The court concluded that *Wyeth*'s "clear evidence" discussion "announce[d] a standard of proof" that is "synonymous with 'clear and convincing evidence'" and required proof showing it "is highly probable that the FDA would not have approved a change to the drug's label." *Id.* at 35a, 37a; see *id.* at 33a-37a. The court further concluded that the relevant preemption determination—which involves "predict[ing] how the FDA would have reacted in a hypothetical scenario" involving a new proposal to strengthen labeling warnings, *id.* at 51a-52a—is a factual determination for a jury, not a legal one for a court. *Id.* at 38a-55a.

Applying those principles, the court of appeals held that summary judgment should not have been granted to petitioner. Pet. App. 55a-74a. As relevant here, the court determined that a "reasonable jury" could conclude that petitioner could have revised the Warnings and Precautions section of its labeling before September 2010. *Id.* at 56a-57a, 67a. A jury, the court reasoned, could find that FDA's 2009 decision to reject petitioner's proposed revision to that section was not based on FDA's determination that the evidence at the

time was insufficient to indicate that Fosamax caused atypical femoral fractures, but rather was based on FDA's dissatisfaction with the proposal's use of the term "stress fractures," which medical practitioners might misunderstand to refer to fractures less serious than the femoral fractures in question, *id.* at 64a-66a. See *id.* at 59a-68a.[9]

SUMMARY OF ARGUMENT

Petitioner provided FDA with the relevant scientific data about Fosamax's risks and, in May 2009, FDA *rejected* petitioner's proposal to add a warning about atypical femoral fractures in the Warnings and Precautions section of Fosamax's labeling. The court of appeals erroneously rejected petitioner's impossibility-preemption defense to respondents' state-law failure-to-warn claims, based on its determination that preemption required petitioner to establish by "clear and convincing" evidence that FDA would have denied a CBE supplement, which the court deemed to be a factual question for a jury to decide. The proper focus here is on whether FDA's May 2009 decision embodied a determination by FDA that insufficient causal evidence existed to warrant strengthening the Warnings and Precautions section of the Fosamax labeling to address atypical femoral fractures. That is a question of law for a court to resolve, not a question of fact for a jury. Moreover, FDA's 2009 decision, construed in light of the governing regulatory regime, and FDA's subsequent

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[9] The court of appeals also concluded that the district court erred in granting summary judgment on claims based on the Adverse Reactions section of Fosamax's labeling before its 2009 revision, Pet. App. 69a-73a, and on non-failure-to-warn claims, *id.* at 74a.

actions show that petitioner could not have altered Fosamax's labeling until late 2010.

A. FDA's May 2009 Complete Response Letter is a legal document reflecting the agency's exercise of legal authority to adjudicate petitioner's regulatory labeling application. The meaning and effect of such agency action is a legal question within the exclusive province of a court. Indeed, courts have long been vested with authority to interpret agency action as a question of law. See, *e.g.*, 5 U.S.C. 706. Judges, rather than lay juries, are best suited to evaluate the scope of an agency's determination because judges are trained and experienced in construing legal documents and are far better equipped to understand agency decisions in light of the governing statutory and regulatory context. Vesting that legal construction in judges familiar with administrative law also fosters the type of interpretive uniformity appropriate when determining the scope and effect of federal agency action. That holds true even when subsidiary factual questions are relevant to the court's legal determination of the meaning and effect of agency action. Cf. *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 388-389 (1996).

B. The court of appeals concluded that *Wyeth* v. *Levine*, 555 U.S. 555 (2009), required a clear-and-convincing-evidence standard, Pet. App. 35a-37a, that a jury must apply in this case, *id.* at 38a-55a. But *Wyeth* addressed distinct circumstances and did not address how to determine the meaning and effect of an *actual* FDA labeling decision. The longstanding rule is that judges, not courts, interpret such agency action as a question of law. Nor does *Wyeth*'s passing reference to "clear evidence" alter the preponderance-of-the-evidence

standard that applies in civil actions involving monetary disputes between private litigants.

C. FDA's May 2009 Complete Response Letter, the relevant regulatory context, and the agency's subsequent actions concerning Fosamax demonstrate that FDA determined that existing information about atypical femoral fractures was insufficient to warrant a change to Fosamax's Warnings and Precautions section. The record amply demonstrates that petitioner could not have updated its labeling until late 2010. Accordingly, respondents' corresponding state-law failure-to-warn claims are preempted.

ARGUMENT

THE COURT OF APPEALS ERRED IN REJECTING PETITIONER'S PREEMPTION DEFENSE

The court of appeals erred in holding that a jury must determine whether FDA's May 2009 decision—which declined to approve petitioner's proposal to revise Fosamax's Warnings and Precautions section to warn against "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft," J.A. 707—preempted respondents' state-law failure-to-warn claims arising from that same type of injury. Where, as here, FDA renders a decision declining to approve a drug-labeling change, the interpretation of that administrative decision and its significance for a failure-to-warn claim are legal questions for a court to resolve, not factual questions for a jury. Moreover, because FDA's action prevented petitioner from modifying the relevant labeling before late 2010, the court of appeals erred in rejecting petitioner's impossibility-preemption defense.

A. Petitioner's Preemption Defense Turns On The Meaning And Effect Of FDA's 2009 Complete Response Letter, Which Are Legal Questions That A Court Must Resolve

"The question for 'impossibility' [preemption] is whether the private party could independently do under federal law what state law requires of it." *PLIVA, Inc.* v. *Mensing*, 564 U.S. 604, 620 (2011). A state-law failure-to-warn claim that rests on the contention that a drug manufacturer failed to provide adequate warnings on drug labeling is therefore preempted if, under federal law, the manufacturer could not have "independently" altered the labeling at the relevant time without FDA's "special permission and assistance." *Id.* at 618-619, 623-624 & n.8. As a general matter, a name-brand drug "manufacturer may only change a drug label after the FDA approves a supplemental application." *Wyeth* v. *Levine*, 555 U.S. 555, 568 (2009). When that is so, potential failure-to-warn claims are preempted.

Some failure-to-warn claims, however, are not preempted under the Court's formulation in *Mensing*. A manufacturer may in certain circumstances submit a CBE supplement, which, upon its receipt by FDA, "permits [the] manufacturer to make certain [safety-based] changes to its label[ing] *before* receiving the agency's approval." *Wyeth*, 555 U.S. at 568 (emphasis added); see pp. 4-5, *supra* (discussing CBE process). FDA may thereafter disapprove the supplemental application and order the manufacturer to cease distributing the drug with such labeling changes. 21 C.F.R. 314.70(c)(7). This Court has accordingly concluded that a brand-name drug manufacturer will establish an impossibility-preemption defense by sufficiently establishing that FDA "would not have approved [the relevant] change to

[the drug's] label[ing]" under its CBE regulation. *Wyeth*, 555 U.S. at 571; see *Mensing*, 564 U.S. at 624 n.8.

In this case, the court of appeals held that the relevant judicial task in resolving petitioner's preemption defense "is to predict how the FDA would have reacted" under the requirements of its "CBE regulation" "in a hypothetical scenario" involving "a different label amendment than the one it actually rejected in [its] May 2009 [Complete Response] letter." Pet. App. 51a-52a. That is incorrect. The threshold inquiry here is whether FDA's May 2009 decision embodied a determination by FDA that insufficient causal evidence existed to warrant strengthening Fosamax's Warnings and Precautions section to address atypical femoral fractures. If FDA's May 2009 decision did reflect such a determination, then petitioner has established an impossibility-preemption defense. And the meaning of FDA's Complete Response Letter is a question of law for a court to resolve, not a question of fact for a jury.

1. Courts, not juries, determine the meaning of federal agency decisions

A federal agency's written decision on a regulatory application is a legal document: an agency action that embodies the agency's exercise of legal authority to adjudicate the application. Cf. 5 U.S.C. 551(6) and (7) (defining agency adjudication). The meaning and effect of such agency action present legal questions within the exclusive province of a court.

When Congress enacted the Administrative Procedure Act (APA), 5 U.S.C. 551 *et seq.*, 701 *et seq.*, it specified that a "reviewing court shall * * * determine the meaning or applicability of the terms of an agency action." 5 U.S.C. 706. That provision reflects the longstanding view that "questions respecting the * * *

terms of any agency action" and the "application" thereof are "questions of law" and therefore matters for "courts * * * to decide." H.R. Rep. No. 1980, 79th Cong., 2d Sess. 44 (1946); see U.S. Dep't of Justice, *Attorney General's Manual on the Administrative Procedure Act* 108 (1947) (APA's review provision "restates the present law").

The legal nature of that inquiry is consistent with this Court's precedent addressing the meaning and effect of a prior judicial adjudication. When issues adjudicated in prior litigation are relevant to factfinding in a subsequent civil action, this Court has held that the question of "[w]hat issues were decided [in that prior] litigation is * * * a question of law" that the trial court must itself decide by examining relevant materials from the prior case. *Emich Motors Corp.* v. *General Motors Corp.*, 340 U.S. 558, 571-572 (1951). That holds true even where a jury must consider "the scope and effect of the former judgment on the case at trial." *Id.* at 572; see *id.* at 568. In such circumstances, the trial court must first determine the prior adjudication's scope and effect before "instruct[ing] the jury" on its legal determination. *Id.* at 571. Just as the scope of a prior judicial adjudication is a question of law for a court to decide, so too is the scope of a federal agency adjudication like the one at issue here.

No sound reason exists for treating the meaning and effect of an FDA administrative determination any differently. Judges, rather than lay juries, are best suited to evaluate the scope of an agency's determination, both because judges are trained and experienced in "[t]he construction of written instruments," *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 388 (1996), and because judges are far better equipped to understand and

interpret agency decisions in light of the governing statutory and regulatory context. Moreover, framing the decision as a question of law to be decided by judges familiar with principles of administrative law will foster the type of uniformity appropriate when determining the scope and effect of federal agency action. See *id.* at 390-391; *id.* at 391 (concluding that uniformity would "be ill served by submitting issues of document construction to juries"). Whether the agency action is a notice-and-comment regulation or something less formal like the adjudicatory decision at issue here, the meaning of agency action is a legal question that a court should decide. See, *e.g.*, *Sprietsma* v. *Mercury Marine*, 537 U.S. 51, 64-68 (2002); cf. *Perez* v. *Mortgage Bankers Ass'n*, 135 S. Ct. 1199, 1208 n.4 (2015) ("[I]t is the court that ultimately decides wh[at] a given regulation means.").

2. Factual findings necessary to interpret a federal agency decision are also matters for courts to resolve

In some contexts, disputed factual questions can be relevant to a court's legal determination of the meaning and effect of an agency decision. For example, if FDA rejected a labeling supplement on the ground that the information supporting it was insufficient to warrant a labeling change, the meaning and scope of that decision can depend on what information FDA had before it. Yet in tort litigation between private parties (which typically will lack compilation of an official administrative record for an FDA decision), litigants may dispute whether a drug manufacturer submitted all material data to FDA. In addition, to the extent that an agency decision read in the proper regulatory context is insufficiently clear, a private litigant might seek to submit extrinsic material to provide further context for interpreting the decision. Where consideration of such

material requires resolution of factual matters for a court to determine the meaning and scope of the agency decision, the court itself should resolve them.

This Court in *Markman* confronted analogous circumstances when it held that "the construction of a patent" is a "purely legal" issue "exclusively within the province of the court." 517 U.S. at 372, 391. The Court reasoned that "judges, not juries, are the better suited" for discerning the meaning of patent terms, even though factual questions involving "credibility determinations" are sometimes "subsumed" within the relevant analysis. *Id.* at 388-389. In other words, the "ultimate issue of the proper construction of a [patent] claim [is] treated as a question of law" for a court to decide, even though "subsidiary factfinding is sometimes necessary." *Teva Pharm. USA, Inc.* v. *Sandoz, Inc.*, 135 S. Ct. 831, 838 (2015). The same rationale applies here. To the extent extrinsic evidence may sometimes be relevant in litigation between private parties to determine the meaning and effect of FDA's agency action, the court's evaluation of such subsidiary facts does not alter the ultimate legal character of the inquiry or the court's exclusive authority to resolve it.

B. The Court Of Appeals Erred In Holding That, Under *Wyeth* v. *Levine*, A Jury Must Resolve Petitioner's Preemption Defense As A Factual Matter Subject To A Clear-And-Convincing-Evidence Standard

The court of appeals should have treated the interpretation of FDA's 2009 labeling decision as a legal question for the courts to decide. As explained further below, the basis for FDA's 2009 Fosamax labeling decision is properly determined as a matter of law from FDA's Complete Response Letter, read in the context of petitioner's underlying labeling supplement and the

governing regulatory framework and related FDA actions. See pp. 30-34, *infra*.

The court of appeals, however, concluded that petitioner's preemption defense presented a question of fact for a jury and this Court's decision in *Wyeth* v. *Levine*, *supra*, required petitioner to provide "clear evidence" from which a jury could find that FDA "would [have] reject[ed] [the] plaintiff's proposed warning" for Fosamax if petitioner had proposed that warning to FDA. Pet. App. 33a, 54a. In addressing that "hypothetical scenario," the court of appeals determined that a jury could reasonably conclude that "FDA rejected [petitioner's] proposed warning about femoral fractures in 2009 not because" FDA deemed the "causal link between Fosamax and fractures" to be insufficient, but because FDA was dissatisfied with petitioner's proposed text. *Id.* at 51a, 64a-65a. There was nothing "hypothetical" about FDA's *actual* 2009 decision in this case, and nothing in *Wyeth* addresses how courts should determine the meaning and effect of such actual agency action.

1. ***Wyeth did not address whether courts or juries should construe an actual FDA decision***

In *Wyeth*, this Court determined that a state-law failure-to-warn claim involving a brand-name drug was not foreclosed by the doctrine of impossibility preemption, because the drug manufacturer had a duty to ensure the adequacy of its own labeling and could have invoked FDA's CBE regulation to update its labeling promptly to provide additional warnings. 555 U.S. at 570-573. The Court recognized that "FDA retains authority to reject [a manufacturer's unilateral] labeling changes made pursuant to the CBE regulation," *id.* at 571, but it explained that Wyeth did "not argue" that

any actual FDA decision had "prohibited" it from strengthening its labeling, *id.* at 572.

The Court instead viewed Wyeth as arguing that FDA had "intended to prohibit it" from changing the labeling when FDA approved prior applications for the relevant drug, a contention that the state trial and supreme courts had rejected. 555 U.S. at 572 & n.5. Thus, without any relevant agency decision at hand, this Court stated that it would not conclude that it was impossible for Wyeth to comply with both federal and state requirements "absent clear evidence that the FDA *would not have approved* a change to [the] label[ing]" in question. *Id.* at 571 (emphasis added). In other words, the Court reasoned that Wyeth needed to make a clear showing that "FDA would have rescinded any change in the label" that Wyeth made through the CBE process in order to establish the impossibility of such a change. *Mensing*, 564 U.S. at 624 n.8. The Court concluded that Wyeth, which did "not argue" that it had provided FDA with an analysis of the "specific dangers" in question, had failed to show that "FDA would have prevented it from adding a stronger warning." *Wyeth*, 555 U.S. at 572-573.

Because *Wyeth* discussed the question whether FDA would have rejected a CBE labeling change *if* the manufacturer in that case had unilaterally made such a change to strengthen its labeling, *Wyeth* did not resolve how to determine the meaning and effect of an actual FDA decision rejecting a proposed labeling change. For that reason, the court of appeals erred in transplanting *Wyeth*'s discussion about the need for "clear evidence" of what FDA "would have [done]" to this context, which concerns the meaning and effect of what FDA *actually did*. This Court has long cautioned that

it is "often misleading" to transplant "[g]eneral expressions" from one opinion "to other facts" because every opinion must be "read in the light of the facts of the case under discussion." *Armour & Co.* v. *Wantock*, 323 U.S. 126, 133 (1944); see *Landgraf* v. *USI Film Prods.*, 511 U.S. 244, 265 (1994) (citing *Cohens* v. *Virginia*, 19 U.S. (6 Wheat.) 264, 399 (1821) (Marshall, C.J.)). *Wyeth* simply does not speak to the circumstances presented here.

2. Any factual findings necessary to resolve a preemption defense need only rest on a preponderance of the evidence

The court of appeals erroneously determined (Pet. App. 35a-37a) that *Wyeth* requires "a factual showing" of impossibility by "clear and convincing evidence" in order to establish a preemption defense. To the extent any factual disputes must be resolved to establish preemption, the proper standard of proof is a preponderance of the evidence.

a. The preponderance-of-the-evidence standard applies in "civil actions between private litigants unless 'particularly important individual interests or rights are at stake'" or a statute prescribes a different standard. *Grogan* v. *Garner*, 498 U.S. 279, 286 (1991); see *Microsoft Corp.* v. *i4i Ltd. P'ship*, 564 U.S. 91, 100-103 (2011) (interpreting patent statute to require clear-and-convincing evidence in certain contexts).[10] Accordingly,

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[10] The clear-and-convincing evidence standard applies when, for instance, the government seeks to terminate an individual's parental rights, *Santosky* v. *Kramer*, 455 U.S. 745, 769-770 (1982), or seeks to deprive an individual of liberty in involuntary commitment proceedings, *Addington* v. *Texas*, 441 U.S. 418, 433 (1979).

in a "typical civil case involving a monetary dispute between private parties," the preponderance standard applies because private litigants should "share the risk of error in roughly equal fashion." *Addington* v. *Texas*, 441 U.S. 418, 423 (1979); see, *e.g.*, *Rivera* v. *Minnich*, 483 U.S. 574, 576, 579 (1987) (action by mother to obtain child-support payments by establishing paternity).

This is a typical private civil action for money damages, and nothing warrants a higher standard of proof to resolve the preemption question here. The Court's preemption decisions do not suggest that a higher evidentiary showing would generally be required where resolution of factual issues is necessary to establish that a state-law duty conflicts with federal law. Although the Court has applied a presumption against implied conflict preemption, that presumption is a "*rule of construction* [that] rests on an assumption about congressional intent," *Arizona* v. *Inter Tribal Council of Ariz., Inc.*, 570 U.S. 1, 13 (2013) (emphasis added), not an evidentiary principle governing the standard of proof. Cf. *Microsoft Corp.*, 564 U.S. at 103 (noting that the existence of a presumption alone does not "establish[] the governing standard of proof"); Fed. R. Evid. 301 (evidentiary presumptions shift the burden of production unless a statute or rule provides otherwise).

b. The court of appeals based its "clear and convincing evidence" requirement on a single sentence in *Wyeth*, Pet. App. 35a & n.94, 37a, in which the Court stated that it "w[ould] not conclude that it was impossible" for Wyeth to strengthen a drug's labeling under the CBE process "absent *clear evidence* that the FDA would not have approved a change to [the] label," 555 U.S. at 571 (emphasis added). But *Wyeth* did not squarely address or definitively resolve the relevant standard of proof

with the phrase "clear evidence." Cf. Pet. App. 28a, 33a-35a (characterizing *Wyeth*'s discussion as "cryptic"). *Wyeth* provides no analysis or any citation to suggest the Court believed it was imposing a higher burden of proof with respect to factual issues, and *Wyeth*'s passing reference to "clear" evidence is not properly read to require one.

This Court has used the term "clear evidence" in contexts in which the Court analyzes preemption issues as a question of law, reflecting an *interpretive* presumption against preemption. See, *e.g.*, *Geier* v. *American Honda Motor Co.*, 529 U.S. 861, 885 (2000) (noting that "a court should not find pre-emption too readily in the absence of clear evidence of a conflict"); *English* v. *General Elec. Co.*, 496 U.S. 72, 86 (1990) ("[W]e find no evidence of a 'clear and manifest' intent on the part of Congress to pre-empt tort claims like petitioner's."). The Court has also held that its use of the even more specific phrase "clear and convincing evidence" in another context involving a question of law should *not* be understood in its "strict evidentiary sense," but merely as a "useful reminder" that a general presumption concerning a *legal interpretation* should control if substantial doubt exists about "congressional intent." *Block* v. *Community Nutrition Inst.*, 467 U.S. 340, 350-351 (1984). The Court in *Wyeth* appears to have similarly used the phrase not as a shorthand for a formal clear-and-convincing evidentiary standard, but merely to indicate that a manufacturer asserting preemption must show that a labeling change was not warranted under the relevant statutory and regulatory framework. If the Court had intended to depart from the preponderance standard that applies to factual issues in almost all

civil actions between private litigants, it presumably would have explained such an unusual departure.

3. Resolving this case does not require factual findings

a. As the case comes to this Court, the preemption question is limited to a situation in which FDA considered the "relevant scientific data" in a prior labeling decision, Pet. i. See Gov't Cert. Amicus Br. 19 n.10; see also Pet. Br. 35 (discussing Sup. Ct. R. 15.2). This case is therefore properly resolved solely on the basis of a legal interpretation of FDA's 2009 labeling decision in light of the governing regulatory regime and subsequent FDA action. Respondents argue (Br. in Opp. 26) that, because petitioner relied below on an internal company document describing a telephone conversation with an FDA employee about petitioner's proposed labeling change, see Pet. App. 17a; J.A. 764-767, a factfinder should assess the reliability and weight of that evidence. But assuming that it would be appropriate to rely on such material in interpreting an agency decision, as explained above (pp. 20-21, *supra*), such a subsidiary factual question would be for courts to resolve in construing the meaning of FDA's 2009 decision; and as explained below (pp. 30-34, *infra*), there is in any event no need here for resort to such evidence because the meaning of FDA's 2009 decision is clear.

To be sure, an actual FDA labeling decision might not in itself resolve preemption if, for instance, FDA did not consider certain safety information in approving name-brand drug labeling or in denying a labeling change because the information was not provided to FDA or because it arose after FDA's decision. In such a situation, a plaintiff could argue that information that FDA did not consider constitutes "newly acquired information," 21 C.F.R. 314.3(b), 314.70(c)(6)(iii)(A), showing

that the drug caused a sufficiently serious hazard to have allowed the manufacturer to update its labeling under the CBE process. Cf. pp. 3-5, *supra*.[11] The proper adjudication of such a contention would need to account for the meaning and scope of any prior FDA labeling decision and the information that FDA previously evaluated in light of the governing statutory and regulatory scheme (matters that the court must resolve, see pp. 18-21, *supra*) in order to determine whether any arguably new information is materially different from the information that FDA previously determined to be insufficient. This case, however, does not present that question.

b. Respondents incorrectly analogize (Br. in Opp. 26; Supp. Cert. Br. 11) this case to *Boyle* v. *United Technologies Corp.*, 487 U.S. 500 (1988). In *Boyle*, this Court discussed the jury's role in evaluating whether a military contractor could raise a federal-common-law defense to a state-law design-defect claim. *Id.* at 504, 507-508, 514; see *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 347 (2001) (describing *Boyle*). That defense required the contractor to make three factbound showings: (1) the United States approved reasonably

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[11] Information—including "new analyses of previously submitted data"—will qualify as "[n]ewly acquired information" only if it "reveal[s] risks of a different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. 314.3(b). Accordingly, nominally "new" information concerning risks of a materially similar type, severity, and frequency as those revealed in information previously evaluated by FDA is cumulative and not "newly acquired information" that could justify a CBE supplement. If for instance, FDA previously determined that that evidence of X was insufficient to warrant a warning about risk Y, the existence of additional but similar information about X would be insufficient to justify a warning.

precise specifications; (2) the allegedly defective military equipment conformed to those specifications; and (3) the contractor warned the United States about the dangers in the use of the equipment that were known to the contractor but not to the United States. *Boyle*, 487 U.S. at 512. In that context, the Court concluded that "whether the facts establish the conditions for the defense is a question for the jury," and it "would be error" for a reviewing court to itself determine that "the defense had [not] been established" unless "no reasonable jury" could have found that "that the Government contractor defense was inapplicable." *Id.* at 514.

Boyle, like *Wyeth*, did not involve the interpretation of an actual federal agency decision. *Boyle* thus does not address the key question here: whether the interpretation of FDA's 2009 decision is a legal inquiry for a court. Nor did *Boyle* address whether a jury should resolve the ultimate matter of preemption when preemption turns on the application of a complex regulatory regime implemented by an expert federal agency like FDA. Cf. *Riegel* v. *Medtronic, Inc.*, 552 U.S. 312, 325 (2008) (observing that a jury that "sees only the cost" of an FDA-approved product in a lawsuit about a plaintiff's injuries is unlikely to "apply cost-benefit analysis similar to that applied by the experts at the FDA"). Certainly, *Boyle* did not hold that the ultimate matter of preemption must always rest with a jury when the parties dispute what might be characterized as underlying factual issues. That question, which is not presented here, warrants further development in the lower courts once this Court has clarified that the preemptive effect of federal agency decisions involves legal questions for courts rather than juries.

C. FDA's May 2009 Decision Rejected A Change To Fosamax's Warnings And Precautions Because The Data At That Time Was Insufficient To Justify A Change

FDA's May 2009 decision rejecting petitioner's proposal to modify Fosamax's Warnings and Precautions section to address atypical femoral fractures was based on the agency's determination that the information about that risk was then insufficient to justify such a warning. That conclusion flows directly from the terms of the agency's May 2009 Complete Response Letter, the relevant regulatory context, and the agency's subsequent actions. Given FDA's determination, respondents' claim that petitioner should have updated its Warnings and Precautions labeling before late 2010 is preempted.

FDA's Complete Response Letter (J.A. 510-513) shows that FDA determined that the existing data for atypical femoral fractures was sufficient to update Fosamax's Adverse Reactions section, but not its Warnings and Precautions section. FDA determined that "atypical and subtrochanteric fractures should be added" as adverse reactions, J.A. 511, reflecting that FDA found "some basis to believe there [wa]s a causal relationship between the drug and the occurrence of th[at] adverse event." 21 C.F.R. 201.57(c)(7).

Petitioner's proposed addition to the Warnings and Precautions section was based on the *exact same risk*. Petitioner proposed a title ("Low-Energy Femoral Shaft Fracture") for its proposed subsection in Warnings and Precautions, J.A. 707, that was identical (with only differing capitalization) to its proposed text for the Adverse Reactions section, J.A. 728. The proposed warning for "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft," J.A. 707, likewise

addressed the same type of adverse reaction that FDA concluded should be added to Fosamax's labeling. See J.A. 512 (FDA's recommendation to add "low energy femoral shaft and subtrochanteric fractures" to Adverse Reaction section). And because both proposed labeling additions addressed the same risk, petitioner proposed adding an explicit cross-reference in the labeling's Adverse Reactions section ("[S]ee PRECAUTIONS, Low-Energy Femoral Shaft Fracture," J.A. 728) that would have directed readers to the more fulsome description of the same hazard proposed for the Warnings and Precaution section.

Under the governing regulations, however, such an adverse reaction is to be elevated to the Warnings and Precautions section only if "reasonable evidence of a causal association with [the] drug" exists. 21 C.F.R. 201.57(c)(6)(i). Here, FDA rejected petitioner's addition because the "*justification* for the proposed [Warnings and Precautions] section language [wa]s inadequate." J.A. 511 (emphasis added). Petitioner had also proposed stating that "[s]ome" of the reported fractures were "insufficiency" "stress fractures," J.A. 707. See p. 8 & n.7, *supra*. But FDA determined that such fractures "may not be clearly related to the atypical subtrochanteric fractures * * * *reported in the literature*," and the associated discussion of stress-fracture risk factors was likewise "not adequately *supported by the available literature and post-marketing adverse event reporting*." J.A. 511-512 (emphases added). FDA's decision thus was based on the lack of adequate data to support a warning.

The court of appeals focused instead on the possibility that "FDA [might have] rejected [petitioner's] proposed warning" because of the warning's use of the term

"stress fractures." Pet. App. 64a-65a. But a Complete Response Letter reflects "FDA's complete review of the *data* submitted"; and FDA's regulations make clear that the letter need not address any "proposed product labeling" if FDA determines that the "data submitted are inadequate." 21 C.F.R. 314.110(a)(2) and (3) (emphasis added). By contrast, if FDA determines that a safety-based labeling change is warranted based on the data, FDA will attempt promptly to identify easily correctable deficiencies in the proposed text and will develop final labeling text with the manufacturer in an iterative process. See pp. 5-6, *supra*. As a result, the May 2009 letter embodies FDA's "recommend[ation]" that petitioner modify its proposed Adverse Reactions text with language (shown here in italics) that FDA itself proposed: "low energy femoral shaft *and subtrochanteric* fracture*s*." J.A. 512 (emphasis added); cf. J.A. 728 (petitioner's proposal). FDA made no similar suggestions for revisions to petitioner's proposed addition in the Warnings and Precautions section because no warning was justified based on the information at the time.

That understanding is reinforced by FDA's subsequent actions in late 2010, when it concluded that the Warnings and Precautions section should be revised. FDA personnel directly edited petitioner's proposed language to remove stress-fracture references deemed insufficiently clear. Pet. App. 22a-23a; see J.A. 547, 549-628 (email with redline showing FDA edits to petitioner's proposed labeling); J.A. 606-607 (FDA edits to proposed warning about atypical subtrochanteric and diasphyseal femoral fractions). No sound basis thus exists for concluding that FDA determined in May 2009 that the data was sufficient to warrant a warning but

that it rejected petitioner's proposal because of petitioner's proposed text. Cf. *Dolin* v. *GlaxoSmithKline LLC*, No. 17-3030, 2018 WL 4001208, at *9 (7th Cir. Aug. 22, 2018) (concluding that it would be "unreasonable" to conclude that FDA rejected a proposed warning because the manufacturer had proposed adding it to the wrong place in the labeling, rather than because FDA had concluded that the warning was not warranted).

Significantly, FDA's own regulations require that the Warnings and Precautions section "must be revised" to add such a clinically significant hazard "*as soon as*" sufficient causal evidence exists. 21 C.F.R. 201.57(c)(6)(i) (emphasis added). And if FDA had "believe[d]" in May 2009 that the "new safety information" that petitioner had submitted "should [have] be[en] included in [Fosamax's] labeling," Section 355(*o*)(4) would have required that FDA "promptly notify" petitioner, 21 U.S.C. 355(*o*)(4)(A), and engage in expedited discussions to revise the labeling, 21 U.S.C. 355(*o*)(4)(B)-(D). Given the statutory and regulatory framework, it would not be reasonable to interpret FDA's 2009 decision as reflecting a determination that a new warning was justified but that FDA rejected petitioner's proposed warning because petitioner's proposed text was inadequate.

Indeed, nearly a year later, in March 2010, FDA announced—after reviewing further information—that it had yet to identify an "increase in [a] risk [of atypical subtrochanteric femur fractures] in women using [bisphosphonates]." J.A. 520. It was only in October 2010—after an external task force had completed its report on the issue—that FDA came to "believe that the information" about atypical femoral fractures should be added to the Warnings and Precautions section and

therefore invoked Section 355(*o*)(4) to revise the labeling for Fosamax and other bisphosphonates. See J.A. 527-528; see also pp. 10-12, *supra*.

In short, FDA's 2009 Complete Response Letter rejecting petitioner's PAS proposal to update Fosamax's Warnings and Precautions section, when read in the proper context of the governing statutory and regulatory regime—as well as FDA's subsequent regulatory actions regarding Fosamax—demonstrate that, in FDA's judgment, an update to Fosamax's Warnings and Precautions section to discuss atypical femoral fractures would not have been called for before late 2010. Accordingly, it would have been impossible under federal law for petitioner to provide such a warning at an earlier time. Any state-law failure-to-warn claim predicated on a state-law duty to provide such a warning is therefore preempted.

CONCLUSION

The judgment of the court of appeals should be reversed and the case remanded for further proceedings.

Respectfully submitted.

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No. 17-290

IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

DORIS ALBRECHT, ET AL.,
Respondents.

On Writ of Certiorari to
the United States Court of Appeals
for the Third Circuit

BRIEF OF *AMICUS CURIAE* AMERICAN ASSOCIATION FOR JUSTICE IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICUS CURIAE*[1]

The American Association for Justice ("AAJ") is a national voluntary bar association founded in 1946 to safeguard the right of all Americans to seek legal recourse for wrongful injury. AAJ's members primarily represent plaintiffs in personal injury actions, employment rights cases, consumer cases, and other civil actions. AAJ works to protect the ability of plaintiffs to vindicate their rights under state tort laws.

As this brief details, in the years since this Court's decision in *Wyeth v. Levine*, 555 U.S. 555 (2009), drug manufacturers have attempted to curtail plaintiffs' state-law rights by arguing for an expansive theory of conflict-preemption that would preempt state laws based on only a hypothetical conflict with federal law. Based on its members' experience with pharmaceutical tort litigation—and its organizational concern for the development of the law in this area—AAJ is well-positioned to explain why such an expansion of federal preemption doctrine is both ill-conceived and contrary to precedent.

INTRODUCTION AND SUMMARY OF ARGUMENT

Over the last decade, this Court has on three separate occasions affirmed that state-law failure-to-warn claims are not preempted where federal law permits a drug manufacturer "to unilaterally strengthen its warning without prior FDA approval." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 624 (2011) (citing *Wyeth v. Levine*, 555 U.S.

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[1] No counsel for a party authored this brief in whole or in part and no person other than *amicus* and its counsel made a monetary contribution to its preparation or submission. The parties' letters consenting to the filing of amicus briefs are on file with the Clerk.

555, 573 (2009) (internal quotation marks omitted); *see also Mut. Pharm. Co., Inc. v. Bartlett*, 570 U.S. 472, 490 (2013).

Despite this clarity, drug manufacturers have repeatedly urged lower courts to divine a rule from *Wyeth* that state-law claims are preempted in cases where the law permitted a company to strengthen its drug's warning label so long as the FDA hypothetically might have rejected that new warning later. This argument not only runs counter to both *Wyeth* and *Mensing*, but also to the cornerstone principle that a state's law is only preempted "to the extent that it *actually* conflicts with federal law." *English v. Gen. Elec. Co.*, 496 U.S. 72, 79 (1990) (emphasis added).

This case presents an opportunity for this Court to reaffirm that there is no such thing as "hypothetical preemption." This Court should clarify that *Wyeth* requires a drug manufacturer to show that the FDA actually rejected the warning at issue—not just that the FDA could or would likely have rejected it. This bright-line rule for impossibility preemption claims is straightforward, easily applied across the entire range of failure-to-warn cases, and faithful to the fundamental rule that state law only gives way when it actually conflicts with federal law. It also avoids any need for the kind of freewheeling speculation about the FDA's hypothetical views that is required by drug manufacturers' reading of *Wyeth*.

Under an actual-rejection standard, preemption does not turn on what the FDA might have done with a particular proposed warning. But if this Court concludes that a defendant's preemption defense in the failure-to-warn context *does* require such an inquiry (as drug manufacturers contend), the final determination should

be submitted to a jury when that defense involves contested questions of fact. Our drug-safety laws frequently require juries to examine complex scientific evidence regarding safety and causation. The inquiry here would be no different: A manufacturer may add a new warning to its label so long as "there is reasonable evidence of a causal association" between a drug and "a clinically significant hazard." 21 C.F.R. § 201.57(c)(6)(i). Determining, based on a weighing of the evidence, whether a sufficient basis for a claimed causal association has been met rests firmly within the jury's traditional realm of competence. The Court should affirm the Third Circuit's decision below denying preemption.

ARGUMENT

I. A state-law failure-to-warn claim should not be preempted on impossibility grounds unless the FDA actually rejected the warning at issue.

This Court has long held that federal conflict preemption will not be found where there is only "a hypothetical or potential conflict" between state and federal law. *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982). Instead, where conflict preemption is alleged, a state's law is only preempted "to the extent that it *actually* conflicts with federal law." *English*, 496 U.S. at 79 (emphasis added). When a party asserts that its state-law obligations were preempted because it was impossible to comply with both state and federal law, the party must demonstrate that it was *actually* "not lawful under federal law . . . to do what state law required." *Mensing*, 564 U.S. at 618.

That rule takes its cue from the text of the Supremacy Clause and our federalist system. Under the Supremacy Clause, state law is preempted only by federal law "made in Pursuance" of the Constitution—

not by extratextual considerations that may require speculation or hypothesis. U.S. const., art. VI, cl. 2. That is why preemption analysis "should not be [a] freewheeling judicial inquiry into whether a state statute is in tension with federal objectives, but an inquiry into whether the ordinary meanings of state and federal law conflict.'" *Wyeth*, 555 U.S. at 588 (Thomas, J., concurring in judgment) (internal quotation marks and citation omitted). When it comes to impossibility preemption, in other words, "state and federal law conflict where it is 'impossible for a private party to comply with both state and federal requirements.'" *Mensing*, 564 U.S. at 618 (quoting *Freightliner Corp. v. Myrick*, 514 U.S. 280, 287 (1995)).

Despite these longstanding principles, litigants in the lower courts have seized on a few sentences from this Court's decision in *Wyeth* to argue for what is effectively a doctrine of hypothetical conflict preemption. In *Wyeth*, this Court held that impossibility preemption does not apply to a failure-to-warn claim where federal law permitted a pharmaceutical company to add the relevant warning to its label. 555 U.S. at 568–73. There, the plaintiff had sued the drug manufacturer Wyeth to argue that it should have adopted a warning regarding the risk of gangrene developing from a particular way of administering a drug. *Id.* at 571. Wyeth argued that it could not have adopted the warning because federal regulations prevented it from changing its drug's label. The Court rejected Wyeth's "cramped reading" of the regulation, and held that the failure-to-warn claim was not preempted. *Id.* at 570–71. The Court noted that the FDA's "changes being effected" process permits drug manufacturers to add new warnings to their labels, which meant that Wyeth "could have . . . added a stronger warning" about the drug in question. *Id.* at 568, 570. In so

holding, the Court briefly noted that even though FDA regulations permit drug companies to add new warnings to their labels, the FDA can later act to reject those changes. *Id.* at 571. But, the Court said, that would not lead to preemption in a failure-to-warn case unless there was "clear evidence that the FDA would not have approved [the] change" in question. *Id.* at 571.

In the years since *Wyeth*, that observation has sparked a novel breed of "hypothetical impossibility" preemption. Drug manufacturers in post-*Wyeth* failure-to-warn cases have advanced a theory of preemption that does not turn on actual impossibility—whether a drug manufacturer could *actually* have added particular warnings to its label—but instead on hypothetical impossibility—whether the manufacturer was right not to include the warning because the FDA *could have and would have* rejected it. *See, e.g.*, *Forst v. SmithKline Beecham Corp.*, 639 F. Supp. 2d 948 (E.D. Wis. 2009); *Dorsett v. Sandoz*, 699 F. Supp. 2d 1142 (C.D. Cal. 2010); *Lofton v. McNeil Consumer & Specialty Pharms.*, 682 F. Supp. 2d 662 (N.D. Tex. 2010); *Hunt v. McNeil Consumer Healthcare*, 6 F. Supp. 3d 694 (E.D. La. 2014); *Koho v. Forest Labs.*, 17 F. Supp. 3d 1109 (W.D. Wash. 2014).

But impossibility preemption does not deal in hypotheticals. This Court should make clear that *Wyeth* did not create a new form of hypothetical conflict preemption. To the contrary, under settled principles of conflict preemption, to win preemption under *Wyeth*'s "clear evidence" standard, a drug manufacturer must show that (1) it attempted to adopt a warning appropriate for the specific injury at issue in the case, (2) the FDA rejected that warning, and (3) no new material evidence arose after that rejection that would have enabled the company

to attempt to add the warning again. As we explain, this standard aligns with this Court's case law, establishes a bright-line rule for preemption claims, and avoids enmeshing lower courts in the type of freewheeling speculation about what the FDA would have done that is called for by drug manufacturers' reading of *Wyeth*.

First, a standard that rejects an inquiry into the FDA's hypothetical actions squares with the Supremacy Clause and this Court's preemption jurisprudence as a whole. As noted above, this Court has rejected the notion of preemption based on "a hypothetical or potential conflict" between state and federal law. *Rice*, 458 U.S. at 659. When it comes to impossibility preemption, "the existence of . . . potential conflicts is entirely too speculative" to warrant preemption. *Exxon Corp. v. Governor of Maryland*, 437 U.S. 117, 131 (1978). Consistent with the text of the Supremacy Clause, for purposes of impossibility preemption state and federal law conflict only "where it is 'impossible for a private party to comply with both state and federal requirements.'" *Mensing*, 564 U.S. at 618 (internal quotations omitted). And "delv[ing] into hypothetical situations" posed by defendants seeking to dodge state-law liability does not present a court with a scenario in which compliance with a state law "requires a violation" of federal law. *Exxon Corp.*, 437 U.S. at 131 (internal quotations omitted); *see also Rice*, 458 U.S. at 659 ("A state regulatory scheme is not pre-empted by the federal antitrust laws simply because in a hypothetical situation a private party's compliance with the statute might cause him to violate the antitrust laws.").

This Court's approach to preemption in the FDA context in particular reinforces this understanding. In *Mensing*, for instance, this Court specifically confirmed

that "[t]he question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it." *Mensing*, 564 U.S. at 620. Impossibility preemption turns, in other words, on what the company "could independently do" at the time in question, not on what might have been the case "depending on the actions of the FDA." *Id.* In *Mensing*, that meant that there was a conflict, and thus preemption, because the drug manufacturer could not have added a warning without express FDA action—so it could not exercise independent authority to comply with state law without running afoul of federal law. *Id.* at 620–21.

But in other contexts, the federal regulatory scheme imposes no similar concrete prohibitions. In cases where the "changes being effected" process is available, for example, there is no conflict *unless and until* the FDA acts—companies are permitted to add a warning to their labels and FDA action is required to remove or prohibit the warning. *See Wyeth*, 555 U.S. at 571; 21 C.F.R. § 314.70(c). In such a case, no conflict preemption exists until the FDA acts because until that point a drug company can "independently" comply with state law by adding a warning to its label. And this is true even if it suspects that the FDA *might* decide not to permit such a warning down the road. *Mensing*, 564 U.S. at 620.

Anchoring conflict preemption to the FDA's actual rejection of a manufacturer's proposed label also advances the aims of the broader regulatory scheme for commercial drugs. As this Court has explained, the principal "premise" of the Food, Drug, and Cosmetic Act is that "manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times." *Wyeth*, 555 U.S. at 579. Given that understanding, "state law

offers an additional, and important, layer of consumer protection that complements FDA regulation"—in the absence of specific FDA regulation, state law (often through common-law tort claims) steps in to supply additional consumer protections. *Id.*

A standard that permits manufacturers to claim preemption even in the absence of FDA action undermines this framework. Restricting preemption to cases where the FDA has actually rejected a manufacturer's proposed warning promotes the incentives for manufacturers to submit new labels with proposed warnings to the FDA—the only way to guarantee either compliance with state law or a valid defense based on conflict preemption. But if manufacturers can claim preemption based on actions the FDA *might* have taken, the incentive to comply with state law is diminished: if a manufacturer believes it has a good argument that the FDA *might* reject the proposed warning, it can avoid complying with state law and reap the benefits of federal preemption, all without risking the possibility that the FDA would, in fact, permit the new warning to issue.

Second, restricting the availability of preemption to cases in which the FDA has acted would provide an administrable bright line for lower courts, avoiding the need for intensive fact development and speculation about the FDA's likely course of conduct.

Post-*Wyeth* cases involving hypothetical-conflict arguments demonstrate just how far some courts have strayed from this Court's "counsel of restraint" when it comes to hypothetical preemption conflicts. *Exxon Corp.*, 437 U.S. at 131. Because a drug manufacturer seeking preemption cannot point to an actual rejection by the FDA that prevented it from adopting the warning at issue, it must ask a court to speculate on what the FDA

would have done had the manufacturer attempted to comply with its alleged state-law duty. In making these arguments, companies have asked courts to consider a wide range of evidence to evaluate whether there might have been a conflict between state and federal law. Among other things, defendants have pointed to:

- The fact that no relevant warning was required for the drug at issue, against a backdrop of periodic reviews by the FDA of evidence with respect to the relevant risks, *Forst*, 639 F. Supp. 2d at 954;
- The fact that a similar warning was required for a similar drug around the time in question, but no new warning was required for the drug at issue, *Hunt*, 6 F. Supp. 3d at 701–02;
- The FDA's decision to require a warning for the prescription version of a drug but not for the over-the-counter version, *Lofton*, 682 F. Supp. 2d at 677;
- A manufacturer's repeated interactions with the FDA in which the FDA did not require an enhanced warning with respect to the drug at issue, *Forst*, 639 F. Supp. 2d at 954;
- The FDA's decision to aim for consistent labels across a particular class of drugs, *Koho*, 17 F. Supp. 3d at 1118–19;
- The FDA's implementation of minor changes in phrasing for required warnings for the drug at issue, *Dorsett*, 669 F. Supp. 2d at 1158 n.14;
- The FDA's rejection of a request to remove a drug from the marketplace, *Lofton*, 682 F. Supp. 2d at 677;

- The FDA's decision to require warnings of the specific symptoms of a disorder, but not a warning that named the disorder itself, *Id.* at 677–78;
- General statements and memoranda issued by the FDA regarding the category of risk at issue, *Dorsett*, 699 F. Supp. 2d at 1157;
- The FDA's responses to citizen petitions addressing the same or related risks for the same or related drugs, *Id.* at 1157; *Lofton*, 682 F. Supp. 2d at 677–78.

Embracing a form of impossibility preemption that turns on these sorts of facts would inevitably open the door to uncabined speculation based on a wide—and ever-increasing—assortment of contextual clues. That transforms *Wyeth*'s passing statement about "clear evidence" into a license to construct elaborate counterfactual scenarios in which the whole range of the FDA's actions—sometimes spanning the course of decades, *see, e.g.*, *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392–96 (7th Cir. 2010)—is mined for hints of regulatory intent. No principled view of conflict preemption supports such an approach.

Indeed, construing facts like these to ascertain preemption demands extensive guesswork. How should a factfinder square, for instance, a statement by the FDA that a class of drugs does not pose a particular risk with its contemporaneous decision to approve a manufacturer's choice to add warnings of that same risk to its drugs' labels? *See Dorsett*, 699 F. Supp. 2d at 1157–58. Should a factfinder consider it more important that the FDA repeatedly rejected efforts to increase required warnings for a particular category of drugs during a certain time period, or that during the same time period the FDA was considering scientific evidence that eventually did lead to

increased warnings? *See Dobbs v. Wyeth Pharm.*, 797 F. Supp. 2d 1264, 1277 (W.D. Okla. 2011) (discussing *Mason*, 596 F.3d at 395). Such "delv[ing]" into speculation about the motives and intentions behind various actions, not to mention the complex facts and standards underlying all of the FDA's decisions, bears little resemblance to the traditional notion that state law will not give way unless it "requires a violation" of federal law. *Exxon Corp.*, 437 U.S. at 131.

Other difficult problems arise with this type of hypothetical-impossibility inquiry. The nature of many failure-to-warn claims means that factfinders will be required to answer not only what the FDA might have done with a given proposed warning, but exactly when the FDA would have done it. It is not uncommon for a failure-to-warn claim to involve a warning that the FDA did eventually adopt after the events giving rise to the particular claim at issue. *See, e.g.*, *In re Actos (Pioglitazone) Prods. Liab. Litig.*, 2014 WL 12776173 (W.D. La. Sept. 5, 2014) (considering argument that defendant should have adopted a warning in 2002 that the FDA began requiring in 2011). If such a claim would be preempted only at the points in time during which the FDA would likely have rejected a given proposed warning, courts could be required to decide exactly when the warning at issue would have been rejected, and when it would have been permitted.

Restricting preemption to cases where the FDA actually rejected a manufacturer's attempt to adopt the warning at issue is not only consistent with settled preemption principles, but it is much simpler to administer. Courts would only have to ask (1) whether the manufacturer attempted to adopt a warning appropriate for the specific injury at issue in the case, (2)

whether the FDA rejected that warning, and (3) whether new material evidence arose after the rejection that would have enabled the company to attempt to add the warning again via the "changes being effected" process. If the answer to either of the first two questions is "no," or if the answer to the third question is "yes," there is no actual impossibility, and therefore no preemption.

This standard would avoid many of the pitfalls that have emerged in the lower courts. The inquiry would not be automatic—courts would still have to examine the language the manufacturer had submitted, and they would have to compare the evidence available at the time of the FDA's rejection to evidence that arose afterward. But those inquiries would be well-defined. A court would not need to consider, for instance, the significance of the FDA's inaction after an important study; its decision to permit or reject a similar warning on a similar drug; or the agency's stated desire to aim for consistent labeling across a specific category of drugs.

The same goes for the need to consider the FDA's rulings on citizen petitions. Although citizen petitions currently constitute a major source of evidence for hypothetical-preemption arguments in the lower courts, they are often unreliable. *See, e.g.*, *Cerveny v. Aventis, Inc.*, 855 F.3d 1091, 1102–03 (10th Cir. 2017) (noting that "brand-name drug manufacturers often file frivolous citizen petitions, asking the FDA to disallow a generic drug's entry into the market," and describing an empirical study suggesting that "citizen petitions are frequently denied because they involve unsupported efforts to stall entry of generic medications into the marketplace"). If preemption turns on the existence of an actual conflict, speculation fueled by resort to this

material would (as it should) be irrelevant to the question of actual impossibility.

What's more, an actual-impossibility standard would deliver little downside. This standard would largely track the same outcomes that have been reached by courts engaging in a more broad-ranging, hypothetical inquiry. Courts have understandably been hesitant to find impossibility-based conflict preemption where the FDA has not actually rejected the specific proposed warning at issue. *See, e.g.*, *Dorsett*, 699 F.Supp.2d at 1157–60; *Forst*, 639 F. Supp. 2d at 952–55; *Lofton*, 682 F. Supp. 2d at 676–78; *Koho*, 17 F. Supp. 3d at 1115–19. And the few cases where courts have found preemption under *Wyeth* have tended to focus on the FDA's actual rejection of the proposed warnings at issue. *See, e.g.*, *In re Depakote*, 87 F. Supp. 3d 916, 922 (S.D. Ill. 2015) ("Abbott tried, on various occasions, to secure approval of a developmental delay warning, and its requests were twice denied by the FDA."); *Dobbs*, 797 F. Supp. 2d at 1276 (finding preemption where the FDA had removed warning language that had been added via the CBE process). An actual-impossibility standard would therefore reinforce what the lower courts already understand—that preemption under *Wyeth* is only appropriate in the face of an actual conflict.

II. In the alternative, if impossibility preemption requires determining the FDA's hypothetical actions, that determination should be made by a jury.

To the extent that this Court holds that an impossibility-preemption defense requires a determination as to what the FDA might have done with a given proposed warning, that determination should be made by a jury. Such a determination could only be made by an inquiry

into complex scientific and case-specific evidence—the kind of inquiry that is firmly within the jury's traditional domain.

Post-*Wyeth* failure-to-warn cases illustrate the point. Because, in these cases, a drug manufacturer did not submit a labeling change to the FDA, it is left to argue that preemption turns on "whether the FDA would have rejected a proposed labeling change, not whether the FDA did in fact issue an explicit rejection." *Seufert v. Merck Sharp & Dohme Corp.*, 187 F. Supp. 3d 1163, 1169 (S.D. Cal. 2016). In the years since *Wyeth*, those courts responding to this hypothetical-impossibility argument have recognized that it is "necessarily fact specific." *Dobbs*, 797 F. Supp. 2d at 1270; *see also In re Depakote*, 87 F. Supp. 3d at 922 (same); *Seufert*, 187 F. Supp. 3d at 1170 (same). The principal inquiry is scientific, not legal, in nature—to determine whether the FDA would permit a given warning to be added, the factfinder must determine whether "reasonable evidence" indicates "an association between a hazard and the drug at issue." *Dobbs*, 797 F. Supp. 2d at 1271 (quoting 21 C.F.R. § 201.57(c)(6)(i)). At bottom, this requires a factfinder "to weigh the evidence submitted by both sides in an attempt to answer the hypothetical question" of what the FDA would have done. *In re: Zofran (Ondansetron) Prods. Liab. Litig.*, 2016 WL 287056, at *3 (D. Mass. Jan. 22, 2016).

Determining what the FDA would have done requires a factfinder to consider the likelihood of various outcomes in a counterfactual scenario. Those counterfactual scenarios involve, at a minimum, the question of what the FDA would have done, based on the available scientific evidence, if a pharmaceutical company had attempted to add a particular warning to its label. *See*,

e.g., *Koho*, 17 F. Supp. 3d at 1115–19; *Lofton*, 682 F. Supp. 2d at 676–78. But counterfactual scenarios can also implicate a host of other key questions—like what the FDA would have done had the manufacturer submitted "information not previously submitted to the FDA indicating the need for a new or strengthened warning." *In re: Zofran*, 2016 WL 287056, at *3.

There is no one-size-fits-all method for resolving this type of inquiry. To answer these questions, a factfinder would need to consider a broad range of relevant facts. This includes "the regulatory history of the drug or drug class at issue," any "temporal gaps between FDA action and accrual of a plaintiff's claims," the existence of relevant "citizen petition submissions and rejections," all "available scientific data," and "whether the FDA has reviewed the particular harm at issue and the consistency of any resulting conclusions." *Seufert*, 187 F. Supp. 3d at 1170.

And these inquiries would often require substantial fact development, including the need to consider expert testimony. *See, e.g.*, *Koho*, 17 F. Supp. 3d at 1117–18. For instance, where a defendant's "preemption argument rests on the premise" that there is no "scientific substantiation" for a "causal link" between a drug and a given risk, expert scientific and/or medical testimony is crucial, if not obligatory. *Id.*; *see also Dobbs*, 797 F. Supp. 2d at 1272 (noting that "[t]he FDA has consistently defined reasonable evidence of a causal association as 'when evidence exists on the basis of which experts qualified by scientific training and experience can reasonably conclude that the hazard is associated with the use of the drug'") (quoting 44 Fed. Reg. 37434, 374634 (June 26, 1979)). The same is true for questions about whether the FDA's statements about that causal

connection in one context necessarily carry over to another. *See Koho*, 17 F. Supp. 3d at 1117–18.

Other fact-specific questions would abound. How might evidence regarding the risks of a drug for a particular demographic group—and the FDA's responses to proposed warnings regarding those risks—imply anything about the suitability for a warning regarding a different demographic group? *See, e.g.*, *Koho*, 17 F. Supp. 3d at 1117–19. And how might the allegedly necessary warnings in a case "compare (or conflict) with . . . label changes and warnings rejected by the FDA" in other cases? *In re: Zofran*, 2016 WL 287056, at *4. And what about "[t]he identity and process by which a labeling change is requested"? *Id.* at *3. That "may be material because the procedural method used could affect the FDA's response to the proposed change." *Id.* at *3.

In some cases, the evidence will point so clearly in one direction that the issue of preemption can be resolved at summary judgment. But in many circumstances, resolving the preemption claim will require the kind of comparative weighing of case-specific scientific evidence that falls comfortably within the jury's traditional role. "In actions at law predominantly factual issues are in most cases allocated to the jury," a principle that "rests on a firm historical foundation." *City of Monterey v. Del Monte Dunes at Monterey, Ltd.*, 526 U.S. 687, 720 (1999). The questions involved in assessing what the FDA would likely have done with a proposed warning are "predominantly factual"—they require the examination of scientific data and testimony, the history of a drug's development, and the context surrounding existing warnings. Analyzing the purposes and effects of the FDA's actions is also properly regarded as a fact-

intensive endeavor; this Court has regarded "complex factual assessments of the purposes and . . . effects of government actions" as core "factual inquiries" that are appropriate for a jury. *Id.* (internal citations omitted).

Indeed, in analogous circumstances, similar fact-finding inquiries are regularly assigned to juries. Take, for instance, the parallel example of drug-fraud tort litigation. In that type of case, an injured plaintiff often claims that a manufacturer's misrepresentation of the safety of a particular drug caused their injury. *See, e.g., In re Neurontin Mktg. & Sales Practices Litig.*, 712 F.3d 21 (1st Cir. 2013); *In re Avandia Mktg., Sales Practices & Prod. Liab. Litig.*, 804 F.3d 633 (3d Cir. 2015). In response, a defendant will frequently raise an affirmative defense that an intervening action of a third party—a doctor who prescribed the drug—breaks the chain of causation. *Id.* at 645 (arguing that "the presence of intermediaries" destroys causation).

Evaluating that defense can involve complicated counterfactual analysis. Juries need to consider and weigh competing evidence regarding how physicians would have seen the drug absent the misrepresentations. *See, e.g., In re Neurontin*, 712 F.3d at 45. Not surprisingly, given the fact-intensive nature of the inquiry, that counterfactual analysis is "a task for the jury." *Id.* at 46; *see also Perez v. Wyeth Labs., Inc.*, 734 A.2d 1245, 1263 (N.J. 1999) ("In each case, a jury must resolve the close question[] of whether a breach of duty has been a proximate cause of harm."). And ultimately, a fact-finder must decide whether the doctor would still have prescribed the drug had she known of the safety problems.

So it is here. When a defendant in a failure-to-warn case raises impossibility preemption as an affirmative

defense, a factfinder must determine what the FDA would have done had it been presented with a particular proposed warning or had it been aware of certain new scientific evidence. The logic is thus no different from that of the intervening-cause affirmative defense: a factfinder must evaluate the likelihood that a third party would have acted in a particular way that would preclude liability the defendant might incur if that same third party were not in the picture. In both contexts, that inquiry often involves a complicated factual analysis of the state of the third party's knowledge of a given drug's risks and benefits at a given point in time.

That the third party in failure-to-warn cases is the FDA rather than a physician or private company is a distinction without a difference. The petitioners in this case raise the fear that a jury would have to "psychoanalyze FDA officials" in an "unbounded inquiry [that] would contravene the presumption that officials exercise their responsibilities faithfully in accordance with the law." Pet. Br. 44. Not so. Because "a presumption of regularity attaches to the actions of Government agencies," *U.S. Postal Serv. v. Gregory*, 534 U.S. 1, 10 (2001), courts can instruct juries that what the FDA would have done can be determined by applying the FDA's standards to the facts at issue in each case. To determine whether the FDA would have rejected a given warning added via the "changes being effected" process, then, a jury could simply evaluate whether there was "reasonable evidence of a causal association" between "a clinically significant hazard" and the drug at issue. 21 C.F.R. § 201.57(c)(6)(i); *see also* 21 C.F.R. § 314.70(c)(6)(iii)(A) (providing that warning labels may be added pursuant to the "changes being effected" process where they "satisf[y] the standard for inclusion in the labeling under § 201.57(c) of this chapter"). That

not only addresses petitioner's fear but demonstrates exactly why it is *unnecessary* for the jury to ask about the mindset of individual FDA officials.

In fact, our drug-safety laws frequently call on juries to examine complex questions regarding drug safety profiles and the state of the FDA's knowledge. For instance, as this Court explained in *Wyeth*, under the FDA's governing statutes, "federal juries will resolve most misbranding claims." 555 U.S. at 570. Finding liability for misbranding, in turn, may require a jury to evaluate whether a company adequately responded to "new and scientifically significant information that was not before the FDA" when it approved the drug at issue. *Bartlett*, 570 U.S. at 487 n.4. None of these tasks requires evaluating the internal psychology of an FDA officer or eschewing the presumption of regularity for federal agency activity. But all, like those here, are appropriate for a jury.

CONCLUSION

The decision below should be affirmed.

Respectfully submitted,

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No. 17-290

In the Supreme Court of the United States

MERCK SHARP & DOHME CORP.,

Petitioner,

v.

DORIS ALBRECHT, ET AL.,

Respondents.

On Writ of Certiorari to the
United States Court of Appeals for the Third Circuit

BRIEF OF THE CATO INSTITUTE AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS

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QUESTION PRESENTED

More than 500 patients allege that Merck's drug Fosamax caused them to suffer atypical femoral fractures. They claim, among other things, that Merck failed to warn adequately of the risk of such serious fractures. The FDA, in 2009, rejected an inadequate warning proposed by Merck, in part because it underplayed and misidentified the risk involved. Merck did not offer an alternative warning addressing the FDA's concerns, and the FDA eventually ordered a stronger warning for the entire class of drugs at issue. Merck now argues that the plaintiffs' failure-to-warn claim is preempted by the FDA's rejection of its proposed warning and hence the company cannot be held liable for failing to provide a different warning before the FDA itself ordered it.

The question presented is:

Whether the Third Circuit accurately assessed the record evidence in concluding that Merck was not entitled to summary judgment on its preemption defense because the company had not sufficiently shown that the FDA would have rejected a properly worded warning about atypical femoral fractures.

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INTEREST OF *AMICUS CURIAE* [1]

The Cato Institute is a nonpartisan public policy research foundation dedicated to advancing individual liberty, free markets, and limited government. Cato's Robert A. Levy Center for Constitutional Studies helps restore the principles of constitutional government that are the foundation of liberty. To those ends, Cato holds conferences and publishes books, studies, and the annual *Cato Supreme Court Review*.

This case interests Cato because liberty is best preserved by enforcing the Constitution's separation of powers, constraints on legislative and executive action, and respect for the dual sovereignty federalism embodied in the Framer's design. Cato also has an interest in challenging government overreach that interferes with tort law and in protecting doctor and consumer access to information that allows people to make informed choices about medical care.

INTRODUCTION

This case turns on whether agency action rejecting a misleading proposed drug label warning – one that misstated, minimized, and sought to deflect blame for the risk of atypical femoral fractures – preempts state-law claims for failure to provide an accurate and proper warning of the true risk.

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[1] No counsel for a party authored this brief in whole or in part, nor did any person or entity, other than *amicus* or its counsel, make a monetary contribution intended to fund the preparation or submission of this brief. This brief is submitted pursuant to the written blanket consent of all parties, on file with this Court.

The background law for this case is the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S. § 301, *et seq.*, which, since its enactment in 1938, has regulated prescription drugs and their labeling. Despite amendments and expansions of FDA authority, Congress expressly has preserved the "widely available state rights of action * * * for injured consumers" "t[a]k[ing] care to preserve state law." *Wyeth v. Levine*, 555 U.S. 555, 567, 574 (2009). Specifically, the Act preempts state law concerning drug labeling only "upon 'direct and positive conflict' with the FDCA." *Id.* at 567 (quoting Drug Amendments of 1968, Pub. L. No. 87-781, § 202, 76 Stat. 780, 793).

Petitioner Merck manufactures Fosamax, a bisphosphonate, commonly used to treat osteoporosis. JA192. The drug works to inhibit natural bone loss that can lead to osteoporosis, but the drug also slows bone repair, which, over time, can lead to a "debilitating fracture in which the thigh bone, or femur, often breaks in two" without any preceding significant trauma or stress. JA288-89, 292. Such fractures are called atypical femoral fractures ("AFFs").

As reports continued to accumulate linking Fosamax use to AFFs, Merck, after some prodding by the FDA, submitted proposed label changes addressing the risk, albeit in a questionable and misleading manner that downplayed the risk by referring to innocuous sounding "stress fractures" and suggesting alternate causalities other than Fosamax. Pet. App. 14a-16a. The FDA rejected the proposed warning in a Complete Response Letter, stating that "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures

that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting." Pet. App. 18a-19a.

Merck did not resubmit revised language for a proposed warning, but the FDA itself eventually announced that it would require all bisphosphonate manufacturers to warn against AFFs. Pet. App. 20a-22a. When petitioner proposed to revise the language drafted by the FDA, adding back references to "stress fractures," the FDA again rejected such revisions, explaining that " 'the term "stress fracture" was considered and not accepted. The Division believes that for most practitioners, the term "stress fracture" represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use.' " Pet. App. 22a-23a.

Respondents, a class of individuals who took Fosamax and suffered AFFs between 1999 and 2010, sued Merck claiming petitioner's failure to add an earlier warning of the risk of AFFs caused their injuries. Pet. App. 75a-95a. The district court granted summary judgment to petitioner on the ground that respondents' failure-to-warn claims were preempted because the FDA would not have permitted Merck to add an earlier warning against AFFs. Pet. App.113a-152, 168a-174a.

On appeal to the Third Circuit, the court of appeals quite sensibly held, under current jurisprudence, that it is a factual question whether the FDA's rejection of the misleading proposed warning is predictive of whether the agency *would have* rejected an

accurate warning, thereby preempting any state-law claims. Pet. App. 4a-5a.

Amicus agrees with respondents that, using conventional preemption analysis from *Wyeth v. Levine*, 555 U.S. 555 (2009), and *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011), the judgment below was correct in denying summary judgment to petitioner Merck. The FDA's rejection of Merck's defective and misleading proposed warning provides no "clear evidence" that it would also have rejected or rescinded a properly worded warning like the one it ultimately required for the class of drugs at issue in this case. Resp. Br. 25-26, 34-50.

Amicus submits this brief, however, to set forth a more straight-forward alternative ground for affirming the decision below: speculation about what the FDA might have done regarding a warning not presented to it does not constitute properly enacted and directly conflicting "Law[] of the United States" entitled to preemptive effect as the "supreme Law of the Land" under the Supremacy Clause. U.S. CONST., Art. VI, cl. 2.

The only relevant "Law" in this case, the FDCA, 21 U.S.C. § 301, *et seq.*, and its amendments, does not contain an express preemption provision applicable to prescription drug labels or the state-law failure-to-warn claims at issue here. Nor does the statute expressly delegate to the FDA the discretion to decide whether and how much state law to preempt when fulfilling the agency's drug-label-related duties under the Act. Indeed, as Congress periodically amended the Act it took pains to disclaim preemption except in the case of a "direct and positive conflict" between the

amendments and a provision of state law. 76 Stat. 780, 793.

Returning to constitutional provisions and principles regarding federal-law supremacy, the nature of federal "Law," and state sovereignty amply supports respondents in this case. The reserved and preexisting authority of the States should not be trumped by inapt speculation regarding what an agency would have done in different circumstances. If agency action is to be deemed preemptive of state law, it must, at a minimum, have directly addressed the conduct in question and directly and positively conflicted with conduct required by state law. Speculation about what conflicting decision the FDA *might have made* in different circumstances that it did not expressly address generates neither a positive nor a direct conflict with state law and does not constitute constitutionally adequate federal "Law" entitled to preemptive force.

SUMMARY OF ARGUMENT

1. Preemption of state law under the Supremacy Clause first and foremost requires the existence of federal "Law" that is said to supersede state law. As explained by Justice Thomas in *Levine*, such a supreme law must be constitutionally enacted in the manner required of all federal laws – by Congress, through the procedures of bicameralism and presentment. In this case, the relevant congressionally enacted "Law" contains no provision expressly preempting state tort law regarding drug label warnings. And while that law also delegates rulemaking power to the FDA, it does not delegate to the FDA the

authority, in the drug labeling context, to preempt state law on its own initiative.

2. Delegated general rulemaking authority alone is insufficient to claim supremacy over state law. While Congress could pass a statute preempting a field within congressional authority to regulate, mere delegation of rulemaking authority does not by itself result in supreme law that would preempt state law. Agencies may execute federal law with greater or lesser discretion, but it is the underlying law itself that carries (or does not carry) preemptive force via the Supremacy Clause. Insofar as the underlying law fails to make the critical preemptive choice of whether and how far to supersede state law, or even to direct the agency itself to flesh out such preemptive choices pursuant to suitable statutory guidance, subsequent agency action cannot preempt on its own. Even valid agency regulations are not law in the constitutional sense but are merely the fleshing out of congressionally enacted law. To the extent that an agency had authority to *create* "Law" via regulation, that would itself violate the constitutional allocation of power among the executive and legislative branches, an issue with which this Court is now grappling in *Gundy v. United States*, No. 17-6086 (argued Oct. 2, 2018).

Even assuming properly delegated authority to an agency to enact rules having the force and status of "Law" via procedures and legislative standards established by Congress, subsidiary agency actions would not necessarily constitute Law entitled to preemptive supremacy. Agency interpretations, sub-regulatory guidance, or discrete ministerial decisions – such as

rejecting a proposed warning for inaccurate and misleading content – are not themselves law but must be traced back to their original source of authority to determine their preemptive effect. *Levine*, 555 U.S. at 587-88, 600-01 (Thomas, J., concurring in the judgment). Speculation regarding what an agency might have done under different circumstances is yet further removed from anything resembling "supreme Law" entitled to preemptive effect.

The decision below in this case is correct under current or alternative jurisprudence and, if anything, too easily accepts the possibility of preemption. The FDA's rejection of Merck's inaccurate proposed warning was not itself "Law" in direct and positive conflict with an obligation for Merck to provide a different and more accurate warning, and thus could not preempt state law imposing liability for failure to provide such a proper warning. Furthermore, it is not even the FDA's action itself that is argued to preempt the state-law claims here, but rather the dubious inference that rejection of the deficient proposed warning predicted subsequent rejection of any further, properly worded, warning not imposed by the FDA itself. Such flawed speculation that the FDA intended to preempt the field while it pondered its next move, like attempts to read the tea leaves of congressional purposes and objectives, is not "Law" or even in the proximity of "Law" qualifying for supremacy under the Constitution.

3. Finally, allowing the inferential claims of supremacy and preemption proposed by petitioner would inevitably be subject to manipulation and abuse. Here, for example, Merck elected to submit a

proposed warning as a "Prior Approval Supplement" ("PAS") needing pre-approval by the FDA rather than immediately adopting a warning subject to subsequent review, as it could have done under the "changes being effected" or "CBE" process. Resp. Br. 4-5, 11-12. That itself introduced a period of delay during which sales of Fosamax would remain undeterred by a more accurate warning.

Compounding its procedural delay, Merck then misstated and minimized the risk through overinclusion of additional and more minor adverse effects – ordinary stress fractures – thereby making the danger seem less severe and masking the correlation between Fosamax and the more specific, serious, and narrow risk of AFFs. Resp. Br. 12 (setting forth Merck's proposed warning). Merck further sought to minimize and deflect the risk by discussing unsupported alternative causalities to imply that its drug was not a significant cause of the risk in question.

The FDA correctly rejected such inaccurate and misleading efforts, but at the cost of (a) further delay and uncertainty regarding the risk of AFFs and (b) further delay in adoption of the stronger and more specific warning eventually required by the FDA. Resp. Br. 15-18. Had Merck at the outset simply adopted a proper warning through the CBE process, doctors and patients would have had more timely warnings and the ability to monitor or minimize the risk by reducing or eliminating long-term consumption of Fosamax.

Merck now seeks to benefit not merely from the delay it caused by proposing a defective warning, but further by claiming that the FDA's rejection of the

inadequate and misleading warning necessarily implies that the agency would have rejected an accurate warning. That is an abuse of preemption doctrine, pure and simple. Such tactics would serve as a roadmap for future manipulation if Merck's approach to preemption were adopted by this Court.

ARGUMENT

I. Preemption of State Law Depends on Conflict with Federal Law Entitled to Supremacy.

A. Federal Law Entitled to Supremacy Must Be Enacted by the Legislative Branch.

As Justice Thomas, concurring in the judgment, explained in *Levine*, 555 U.S. at 582-88, preemption is a function of the Supremacy Clause, which provides:

> This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any state to the Contrary notwithstanding.

U.S. CONST., Art. VI, cl. 2. Preemption thus depends on the existence of properly enacted federal "Law" prohibiting or irreconcilably conflicting with state law. *Levine*, 555 U.S. at 585-86 (Thomas, J., concur-

ring in the judgment); *Williamson v. Mazda Motor of America, Inc.*, 562 U.S. 323, 340 (2011) (Thomas, J., concurring in the judgment).

This fundamental restraint on preemption – insisting that it be tied to "Law" properly enacted pursuant to the Constitution, recognizes the pre-existing sovereignty of the States, the intentional limits on the powers of the federal government, and the important procedural hurdles of bicameralism and presentment from Article I, § 7, cls.2-3, placed in the path of the exercise of federal power. *INS v. Chadha*, 462 U.S. 919, 945-46, 951, 959 (1983). Accordingly, "in order to protect the delicate balance of power mandated by the Constitution, the Supremacy Clause must operate only in accordance with its terms." *Levine*, 555 U.S. at 585 (Thomas, J., concurring in the judgment).

In this case there is no serious dispute that nothing in the FDCA or its amendments expressly preempts state tort law regarding drug warnings, or that the Act was designed to coexist with such state law. Resp. Br. 3-7. Likewise, there is no dispute that nothing in the Act or the regulations thereunder is in direct and positive conflict with a failure-to-warn claim given that drug companies may unilaterally add a warning to their labels, subject to *post hoc* review by the FDA. 21 C.F.R. § 314.70(c)(6)(iii)(A).

The source of alleged conflict here and in similar cases comes not from a statutory command enacted by Congress or from direct FDA rulemaking, but from a hypothetical future decision by the FDA that supposedly would have prohibited a proper warning as required by state law. The ultimate source of alleged preemption is thus the implausible *inference* that, be-

cause the FDA rejected Merck's initial misleading warning, *any* further warning would have been rejected.

However far the claim of preemption "wander[ed]" from the statutory text in *Levine*, 555 U.S. at 583 (Thomas, J., concurring in the judgment), the claim in this case goes well over the horizon of any statutory connection. It is not Congress's nebulous purposes and objectives we are discussing here, or even the expressly stated, but new and non-binding, agency purpose at issue in *Levine*. 555 U.S. at 575-79 (discussing and rejecting agency preamble claiming that approved labels constitute a ceiling as well as a floor). Rather, preemption here is being inferred from dubious speculation that the agency had the unspoken purpose and objective to preempt *all* future warnings based merely on its rejection of Merck's defective warning. Just as "[c]ongressional and agency musings * * * do not satisfy the Article I, § 7, requirements for enactment of federal law," 555 U.S. at 587 (Thomas, J., concurring in the judgment), surely speculation concerning what the FDA might have done regarding a warning that was not before it does not qualify as federal law capable of preempting state law under the Supremacy Clause. And even if it were factually plausible, such implied agency intent to bar all subsequent warnings related to a class of risks is not "Law" and does not reflect or execute any statutory command adopted by Congress.[2]

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[2] As in *Levine*, this case does not raise any questions concerning an express agency regulation purporting to forbid manufacturers from adding warnings under particular circumstances. 555 U.S. at 576; *id.* at 583 (Breyer, J., concurring). Such a reg-

B. Congress Has Not Delegated to the FDA Authority to Preempt State Law.

A further problem with the purported preemptive effect of speculation regarding future FDA action is that Congress has not delegated to the FDA preemptive discretion in connection with prescription drug labels. Unlike with medical devices or in other statutes, where Congress has included preemption clauses and directed the agency to define the scope of such preemption, here Congress made no such grant of authority.[3] This Court in *Levine* already has rejected the FDA's claim of power to expand the preemptive scope of its drug labelling authority to make it a ceiling as well as a floor, 555 U.S. at 574-75. Absent such express authority in the statute and a guiding principle reconciling state and federal interests, the FDA would have no discernable standards by which to measure any assertion of preemptive supremacy and would essentially be making its own law in an area of constitutional sensitivity.

Not only would such intrusive law be imposed without the protections of bicameralism and presentment, it would likewise violate the separation of

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ulation, if adopted through proper procedures and reviewed for consistency with the underlying statute and other constitutional constraints, might well have enough connection with the FDCA to be entitled to preemptive force. Here, no regulation or any other agency action precluded Merck from curing the defects in its proposed warning identified by the FDA and resubmitting, or even implementing directly through CBE procedures, a warning such as the one ultimately approved.

[3] *See Levine*, 555 U.S. at 576 & n. 9 (giving examples of statutes expresaly authorizing agencies to preempt state law).

powers principles underlying the non-delegation doctrine. *See, e.g., Department of Transp. v. Association of Am. R.R.*, 135 S. Ct. 1225, 1244 (2015) (Thomas, J., concurring) ("[T]he separation of powers is, in part, what supports our enduring conviction that the Vesting Clauses are exclusive and that the branch in which a power is vested may not give it up or otherwise reallocate it."); *see also Whitman v. American Trucking Ass'ns*, 531 U.S. 457, 486-87 (2001) (Thomas, J., concurring) ("I am not convinced that the intelligible principle doctrine serves to prevent all cessions of legislative power. I believe that there are cases in which the principle is intelligible and yet the significance of the delegated decision is simply too great for the decision to be called anything other than 'legislative.'"). And where the alleged preemption comes from speculative inferences of what the FDA might have done in different circumstances, rather than from an express and specific assertion of preemption of a particular warning required by the State, the delegation concerns multiply even further.

Any suggestion that the FDA has implicitly preempted a state-law claim for failure to warn should be viewed with deep skepticism in order to avoid thorny constitutional problems of delegation of legislative authority. Surely the decision to supersede the authority of sovereign States is fundamentally legislative in nature and, if permissible at all, *Whitman*, 531 U.S. at 487 (Thomas, J., concurring),

requires an express delegation of such authority and significant direction regarding its exercise.[4]

II. A Broad Preemptive Reading Here Would Invite Abuse.

In addition to distorting the constitutional justification for preemption, the preemption theory proposed by Petitioner is subject to manipulation and abuse. If the FDA's rejection of a defective proposed warning can have preemptive force regarding any and all alternative warnings that could have and should have been used, then every drug company would have an incentive to propose warnings that are designed to be rejected and cause delay. This case is the perfect example.

Functionally, petitioner's theory is that any tangential proposed warning relating to a broadly defined risk is enough to preempt failure-to-warn

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[4] At a minimum, a strict test of impossibility should be applied where the only claim of preemption is inconsistency with agency action not even embodied in formal rulemaking. And even then, the supposedly preemptive directive should be explicit in its preemptive intent and well-grounded in the agency's statutory authority. In this case, of course, even if there were unequivocal statements forbidding Merck to adopt any revised warning at all, regardless of content, Merck could still comply with both state and federal law by suspending sales of its drug pending further investigation of the emerging risks. As Justice Thomas has recognized, *Levine*, 555 U.S. at 592-93 (Thomas, J., concurring in the judgment), the FDCA does not create a free-standing right to sell prescription drugs so long as their label is approved by the FDA. That is the inevitable implication of *Levine*'s conclusion that the labelling requirements of the FDCA set a floor, not a ceiling, and its rejection of the FDA's assertion to the contrary.

claims for any related risk until the FDA itself comes up with an adequate warning. Indeed, it is precisely because the FDA found Merck's warning defective that Merck now claims immunity from suit for its failure to propose a better warning. One might suspect – and a jury could certainly find – that Merck sought pre-approval using a defective warning precisely to delay the time when a more effective warning – likely to reduce the use of Fosamax – was put in place.

For example, while Merck had ample information and could have used the CBE process immediately to adopt a warning comparable to the one ultimately drafted by the FDA, it instead chose the slower route of proposing a warning under the PAS process and waiting for the FDA to react. Furthermore, the warning it then proposed was both deficient and self-serving in several ways. First, by repeatedly describing the relevant risk as involving stress fractures, Merck's proposed warning downplayed the severity of the danger and would have reduced the effectiveness of the warning and hence the impact on sales. The FDA recognized the misleading quality of the language Merck proffered when later rejecting its attempts to reincorporate such language into the warning eventually required by the FDA. Pet. App. 22a-23a

Second, the overbroad description of the risk as involving stress fractures allowed Merck to mask the actual correlation between Fosamax and AFFs by including a much larger group of adverse events that had little or nothing to do with Fosamax. By substantially expanding the events to include such more

common types of mild fractures, Merck could pretend that the correlation between all fractures and Fosamax was weak. Of course, when the literature and the studies were reviewed with a narrower focus on the particular and severe AFFs, the data told a more troubling story regarding the risk associated with long-term use of Fosamax. *See* Pet. Br. 14 (discussing task force's reassessment of prior studies focusing on narrowly defined AFFs). The consequence of using an improperly broad category of adverse events is that it made it more difficult for the FDA to evaluate the need for a warning, made it less likely that the FDA would approve the flawed warning, and ensured, at a minimum, further delay. Not surprisingly, all this inured to the commercial benefit of Merck by delaying any loss of sales that would come from adoption of an effective warning.

Third, Merck also included a disingenuous paragraph listing a string of alternate causalities for stress fractures (though not for the more severe AFFs) in a bid to again minimize the risk posed by its drug. Such minimization would again diminish the effectiveness of the proposed warning and, at a minimum, potentially delay a patient going off Fosamax while such other possibilities were investigated. As the FDA noted when rejecting Merck's proposed warning, the misleading discussion of alternate causalities had no basis in the literature.

Each of these factors – using the slower PAS process rather than the immediate CBE process; using misleading language to suggest minor risk, to mask proper analysis of the actual risk, and to distract from the risk of its drug by proposing alternate cau-

salities; failing to correct the identified deficiencies in response to the FDA's Complete Decision Letter; and then attempting to reincorporate its misleading language into the FDA's own proposed warning – raises a disturbing inference of Merck's having gamed the system. Certainly, a jury could find that Merck submitted a defective and misleading warning in order to cause delay, sabotage the likelihood of approval, and undermine any potential warning that might be approved, all while preserving a claim of preemption.

If preemption is found here, then the proliferation of proposed warnings designed to obfuscate or to be rejected and thereby delay adoption of a stronger warning would create a win-win for the drug companies, but unfortunately a lose-lose for state law and the consumers such law seeks to protect.

CONCLUSION

For the foregoing reasons, this Court should affirm the judgment of the court of appeals.

Respectfully submitted,

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No. 17-290

In the Supreme Court of the United States

MERCK SHARP & DOHME CORP., PETITIONER,

v.

DORIS ALBRECHT, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

BRIEF AMICI CURIAE OF VIRGINIA, CALIFORNIA, CONNECTICUT, DISTRICT OF COLUMBIA, ILLINOIS, INDIANA, IOWA, KENTUCKY, MARYLAND, MASSACHUSETTS, MINNESOTA, MISSISSIPPI, MONTANA, NEW JERSEY, NEW MEXICO, NEW YORK, NORTH CAROLINA, NORTH DAKOTA, OREGON, PENNSYLVANIA, RHODE ISLAND, VERMONT, AND WASHINGTON IN SUPPORT OF RESPONDENTS

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INTEREST OF THE AMICI CURIAE

"[B]oth the Federal Government and the States wield sovereign powers." *Murphy* v. *National Collegiate Athletic Ass'n*, 138 S. Ct. 1461, 1475 (2018). Valid federal statutes are, of course, "the supreme Law of the Land . . . any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const. art. VI, cl. 2. But preemption analysis "start[s] with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Wyeth* v. *Levine*, 555 U.S. 555, 565 (2009) (quotation marks and citation omitted). States also have a strong interest in preserving state laws that protect their citizens from unsafe drugs and providing remedies to consumers injured by drugs. The amici States thus have a substantial interest in the Court's resolution of this case.

SUMMARY OF ARGUMENT

Unlike other federal statutes regulating medical devices, vaccines, and over-the-counter drugs, the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301 *et seq.*, contains no provision expressly preempting state tort claims. In *Wyeth* v. *Levine*, 555 U.S. 555 (2009), the defendant company "abandoned" any field preemption argument, *id.* at 560, and this Court concluded that state tort claims do not categorically "stand as an obstacle to the accomplishment of Congress' purposes in the FDCA." *Id.* at 581.

That leaves one remaining form of preemption: impossibility. In *Wyeth*, this Court considered and rejected an impossibility-preemption argument under the same statute at issue here because the party urging preemption had "failed to demonstrate that it was impossible for it to comply with both federal and state requirements." 555 U.S. at 573. The Court acknowledged that the result may have been different had the company presented "clear evidence that the FDA would not have approved a change to [the drug's] label." *Id.* at 571. But the Court perceived no such evidence in the record before it, *id.* at 572, and it emphasized that "[i]mpossibility pre-emption is a demanding defense," *id.* at 573.

In this case, petitioner seeks to convert the Court's careful qualifier into a sweeping exception that threatens to destroy the underlying rule. In *Wyeth*, the Court squarely rejected the company's possibility-of-impossibility defense, concluding that it was not enough to suggest that FDA *might* have rejected a proposed warning when neither the alternative warning nor the information that would have supported it had been presented to the agency. See *Wyeth*, 555 U.S. at 572. Yet here, petitioner urges preemption of claims arising out of its failure to disclose *one* type of risk (atypical femoral fractures) based on a previously submitted warning to the FDA about a *different* type of risk (stress fractures). See U.S. Br. 8 n.7 (distinguishing between the more common stress or "fatigue" fractures and insufficiency fractures).

Petitioner's argument is inconsistent with this Court's reasoning in *Wyeth* and would upset Congress' careful balance between federal and state regulatory authority in this important area of traditional state concern. See *Wyeth*, 555 U.S. at 578 (noting that "FDA traditionally regarded state law as a complementary form of drug regulation"). Petitioner's proposed rule disregards the cornerstone of this Court's preemption jurisprudence (the presumption against preemption) and replaces it with a presumption of preemption in any situation where the FDA previously declined a request for a label change. Adopting such a rule would unduly circumscribe the state remedies available to injured consumers and shift the costs of injuries from those whose products inflict them to the States and communities where injured people live and work. It also would limit the efficacy of state law rules designed to ensure that companies internalize the costs of their business decisions, including the decision to withhold safety information from the public.

For these reasons, the amici States urge this Court to affirm the decision below

ARGUMENT

"Impossibility pre-emption is" and should remain "a demanding defense." *Wyeth* v. *Levine*, 555 U.S. 555, 573 (2009). It is "a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times." *Id.* at 570–71 (emphasis added). "[T]he very idea that FDA would bring an enforcement action against a manufacturer for

strengthening a warning . . . is difficult to accept." *Id.* at 570 (emphasis added); see *id.* (emphasizing that "neither Wyeth nor the United States has identified a case in which the FDA has done so"). And this Court has emphasized that state tort actions play a critical role in "uncover[ing] unknown drug hazards" by "motivat[ing] injured persons to come forward with information." *Id.* at 579.

All of those considerations counsel against preemption here. Drug manufacturers have managed to comply with both federal drug labeling obligations and state common law for almost 80 years. Far from presenting the kind of irreconcilable obligations that justify a categorical rule of preemption, the availability of common law tort suits complements and completes the federal scheme. See *Wyeth*, 555 U.S. at 578 (emphasizing that "[t]he FDA has limited resources to monitor the [then] 11,000 drugs on the market"). Although petitioner proposed a warning about one type of risk (stress fractures), it did not propose a warning sufficient to inform consumers about the risk that forms the basis of respondents' state law tort claims (atypical femoral fractures). Accordingly, the court of appeals correctly rejected petitioner's impossibility-preemption defense.

I. Fundamental federalism principles counsel against petitioner's broad view of impossibility preemption

The Constitution expressly reserves to the States or the people all powers not delegated to the federal

government. See U.S. Const. amend. X. "The States [thus] retain substantial sovereign authority under our constitutional system," and "[t]his federalist structure of joint sovereigns preserves to the people numerous advantages." *Gregory* v. *Ashcroft*, 501 U.S. 452, 457–58 (1991). As especially relevant here, "a decentralized government . . . will be more sensitive to the diverse needs of a heterogeneous society"; "allows for more innovation and experimentation in government"; and "makes government more responsive by putting the States in competition for a mobile citizenry." *Id.* at 458.

All of those interests go unserved when state laws are preempted. This concern may have had less salience in the early years of our Republic when federal law was "generally interstitial in its nature." Henry M. Hart, Jr. & Herbert Wechsler, *The Federal Courts and the Federal System* 470 (2d ed. 1973). But today's Congress asserts vast authority over many areas of everyday life, see, *e.g.*, *Gonzales* v. *Raich*, 545 U.S. 1, 17 (2005), and the opportunities to preempt state law have correspondingly broadened.

As a result, the Court has adopted a variety of interpretive rules that protect state authority. For example, the Court requires a "plain statement" before it will conclude that Congress meant to "upset the unusual constitutional balance of federal and state powers." *Gregory*, 501 U.S. at 460–61. The Court will not read a federal statute as abrogating a State's immunity from suit unless Congress makes such an "intention unmistakably clear in the language of the statute."

Atascadero State Hosp. v. *Scanlon*, 473 U.S. 234, 242 (1985). And, as relevant here, any preemption analysis "start[s] with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Rice* v. *Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947).

There is nothing atextual about this method of interpretation. To the contrary, these rules—including the presumption against preemption—serve a crucial structural function. They help to safeguard the Founders' overarching constitutional design—a design crafted to give States a significant role in day-to-day governance. *Medtronic, Inc.* v. *Lohr*, 518 U.S. 470, 485 (1996) ("[B]ecause the States are independent sovereigns in our federal system, we have long presumed that Congress does not cavalierly pre-empt state-law causes of action.").

These structural benefits redound to Congress and the States alike. The presumption against preemption rests on the assumption that Congress—not a court—has the power to dictate the bounds of congressional purpose. See *Gade* v. *National Solid Wastes Mgmt. Ass'n*, 505 U.S. 88, 111 (1992) (Kennedy, J., concurring in part, concurring in judgment) (emphasizing that "it is Congress rather than the courts that preempts state law"). And without this safeguard, States themselves will often lack political recourse. Both practical realities and this Court's precedent mean that "the political process" provides the primary "protection of the States against intrusive exercises of

Congress' Commerce Clause power." *Gregory*, 501 U.S. at 464. But States (and their citizens) cannot use the political process to protect against overly broad preemption of state tort law if courts accept the invitation to craft broad rules of preemption that are untethered to the text of any congressional act.

This case illustrates the point. "If Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express preemption provision at some point during the FDCA's 70-year history." *Wyeth*, 555 U.S. at 574. But adopting a sweeping form of obstacle or impossibility preemption here would presume that Congress, although silent on the issue, would have wanted state law displaced. Such an approach conflicts with basic canons of statutory construction and the judiciary's institutional role. It also would undermine the protections the political process is designed to afford the States—especially where, as here, the argument for preemption is based not on the text of any congressional enactment but rather on the everyday actions of a federal agency. See *Hines* v. *Davidowitz*, 312 U.S. 52, 75 (1941) (Stone, J., dissenting) (emphasizing that "it is difficult to overstate the importance of safeguarding against . . . diminution of state power by vague inferences as to what Congress might have intended if it had considered the matter or by reference to our own conceptions of a policy which Congress has not expressed").

II. Regulation of consumer safety is an area of traditional state concern

"[I]n all pre-emption cases," this Court "start[s] with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Wyeth*, 555 U.S. at 565 (internal quotation marks and citations omitted). This is "particularly" so where "Congress has legislated in a field which the States have traditionally occupied." *Id.*

States have long regulated in the area of drug labeling. The duty to warn patients and physicians about emerging safety risks predates—by decades—the advent of federal regulation of drugs. See, *e.g.*, *Thomas* v. *Winchester*, 6 N.Y. 397 (1852); see also *Lohr*, 518 U.S. at 485 (noting the "primacy of state regulation of matters of health and safety"). When the FDA first emerged on this scene, it too understood its mandate to be wholly consistent with this longstanding state duty. See, *e.g.*, 44 Fed. Reg. 37,434, 37,447 (June 26, 1979) (FDA labeling decisions do not "influence civil tort liability of the manufacturer"); 59 Fed. Reg. 3,944, 3,948 (Jan. 27, 1994) (recognizing that "product liability plays an important role in consumer protection," in notice proposing rules to protect the identities of individuals reporting adverse drug reactions); 63 Fed. Reg. 66,378, 66,384 (Dec. 1, 1998) (observing that FDA labeling "regulations establish the minimal standards necessary, but were not intended to preclude the states from imposing additional labeling requirements," in FDA's final guidance on prescription drug labeling).

Against this backdrop of deeply rooted state tort law, Congress chose not to include preemptive language in the FDCA. Nor did it include such language in the years to follow, though "[j]udgments against manufacturers of various FDA approved products were by no means rare." Robert B. Leflar & Robert S. Adler, *The Preemption Pentad: Federal Preemption of Products Liability Claims after* Medtronic, 64. Tenn. L. Rev. 691, 704 (1997). Although Congress did opt to preempt state law requirements for medical devices and vaccines,[1] it left state requirements relating to pharmaceutical labeling untouched.

In 1962, Congress enlarged the FDA's powers and shifted the burden of proof from the FDA (to prove the drug would cause harm) to the manufacturer (to prove the drug was safe). Here too, Congress could have added a provision preempting state law. But, instead, Congress "took care to *preserve* state law" with a new "saving clause, indicating that a provision of state law would only be invalidated upon a 'direct and positive conflict' with the FDCA." *Wyeth*, 555 U.S. at 567 (citing FDCA § 202).

As this Court has explained "[t]he case for federal pre-emption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided

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[1] In contrast to the FDCA, which contains no express preemption provision, Congress chose to expressly preempt state actions based on injuries arising from medical devices, 21 U.S.C. § 360k(a), and vaccines, 42 U.S.C. §§ 300aa-22(b)(1) and (e); along with state positive-law requirements with respect to over-the-counter drugs, 21 U.S.C. § 379r(a).

to stand by both concepts and to tolerate whatever tension there is between them." *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 166–67 (1989) (internal quotation omitted). Here, the long history of state tort litigation against manufacturers of prescription drugs—and Congress's repeated failure to amend the FDCA in response—"adds force to" the conclusion that Congress did not intend to preempt such litigation in the ordinary case. *Bates* v. *Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005).

III. Petitioner's proposed rule would disturb the balance between state and federal regulation that this Court struck in *Wyeth*

1. Petitioner proffers the following rule: "If a manufacturer proposes to warn about a risk, discloses what it knows about that risk, and gets rebuffed by the FDA, failure-to-warn claims against it are preempted as a matter of law." Pet. Br. 20. But respondents dispute that the warning petitioner presented to the FDA (stress fractures) encompassed the harm underlying respondents' state tort law claims (atypical femoral fractures). What is more, petitioner has not demonstrated that the label change it proposed to the FDA would have satisfied its state law duty to warn. Any construction of the test that would allow petitioner to prevail without such a showing would slight the presumption against preemption and the critical role of state tort law in this area.

Petitioner's sweeping approach to impossibility preemption also raises a host of other problems. For

one thing, it would create perverse incentives on the front end. Under petitioner's theory of preemption, the FDA's rejection of a proposed warning based on inadequate evidence would bar later tort claims—even if the inadequate evidence was itself the result of the company's own lack of diligence. Such an approach would reward manufacturers who fell short in their efforts to collect information about a particular risk and create incentives to learn as little as possible before proposing label changes to the FDA. It would also undercut state law warning requirements whose application is predicated on constructive (rather than actual) knowledge.[2] And it would create an immunity from state tort liability based on something that only the manufacturer can ultimately control: "what [*the manufacturer*] knows" about a given risk. Pet. Br. 20. That cannot be what Congress intended.

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[2] See, *e.g.*, *Nicholson* v. *American Safety Utility Corp.*, 476 S.E.2d 672 (N.C. App. 1996) (interpreting N.C. Gen. Stat. Ann. § 99B-5 to require seller to warn of any hazard associated with use of product if seller has actual or constructive knowledge of particular threatening characteristic of product); *Frey* v. *Montgomery Ward & Co.*, 258 N.W.2d 782, 788 (Minn. 1977) (stating that "where the manufacturer or the seller of a product has actual *or constructive* knowledge of danger to users, the seller or manufacturer has a duty to give warning of such dangers") (emphasis added); La. Stat. Ann. § 9:2800.57 ("[A] product is unreasonably dangerous because an adequate warning about the product has not been provided if . . . the product possessed a characteristic that may cause damage and the manufacturer failed to use reasonable care to provide an adequate warning of such characteristic"); Miss. Code Ann. § 11-1-63(c) (adopting actual or constructive knowledge standard for product liability under failure-to-warn theory).

Petitioner's proposed rule also would remove any incentive to continue gathering information after the FDA has declined to approve a label change. As the Federal Government seems to acknowledge, see U.S. Br. 27–28, a manufacturer might discover new evidence about a risk after the FDA has already rejected a label change regarding that risk. Depending on the nature of the new information, the FDA's earlier rejection may no longer signal the agency's ongoing opposition to future label changes. Nevertheless, here too, petitioner's proposed rule would assume impossibility because the company has made a single, unsuccessful attempt to amend the drug's label—even when new risk information has changed the underlying calculus.[3]

Both of these problems present opportunities for gamesmanship. For example, a company seeking to avoid state tort liability could propose a label change that it knows the FDA will reject based on then-insufficient evidence. Though designed for failure, that proposal would head off any potential future claims based on the company's failure to warn should evidence of that risk later accumulate. Even worse, a company could propose a change framed in terms that it knows the FDA will reject with the goal of preempting any subsequent state law claims that it can stuff under the same general umbrella. This Court should be wary of a rule that would permit a regulated entity to

[3] For example, more than 200 plaintiffs involved in this litigation were injured after the FDA's rejection of petitioner's label change. Even if relevant, the FDA's decision in May of 2009 may not necessarily indicate its position 16 months later when some plaintiffs incurred injuries. J.A. 26–27, 40.

manufacture impossibility preemption by strategically submitting overbroad or inaccurate warnings.

Finally, petitioner's application of its proposed rule vividly illustrates the rule's ambiguities and its potential for mischief. It is straightforward enough to determine whether the FDA rejected a specific proposed warning. Petitioner's proposal, however, sweeps much broader and would result in preemption whenever a manufacturer "proposes to warn about *a risk*." Pet. Br. 20 (emphasis added). But that formulation skates over a host of difficult questions about how (and how broadly) courts are to define the word "risk" in this context. In particular, it tells us nothing about what "risk" the company aimed to disclose and thus which warnings the FDA refused to permit.

These details matter. The parties to this case actively dispute whether petitioner's proposed label change would have warned respondents about the risks that ultimately resulted in their injuries.

Just as important, the parties also dispute whether the label that petitioner proposed would have satisfied the state law duty to warn. If the proposed label would have satisfied the state law duty in this case, the FDA's rejection might constitute some evidence that petitioner could not have complied with both its state and federal obligations.[4] But if the proposed changes would not have satisfied the state law

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[4] That said, even a square FDA rejection of *one* formulation that would have satisfied the duty to warn imposed by state law would not necessarily mean that FDA would have rejected *any* formulation that satisfied the state law duty.

duty to warn, the FDA's rejection of *those* changes would have little bearing on the preemption question at hand. See *Wyeth*, 555 U.S. at 571 (framing the issue as whether FDA "would not have approved" the type of change that plaintiffs argue state law required). A party should not be able to claim impossibility preemption by showing that federal regulators rejected a warning that would not have satisfied the state law duty that that party stands accused of violating. Absent a showing that the federal regulators did (or obviously would have) rejected a warning that satisfied state law, a manufacturer cannot show that compliance with both state and federal law is actually impossible.

The Court's decision in *Wyeth* resolves this case, and because the manufacturer can comply with both state and federal law, there is no preemption here. If the Court is inclined to clarify the rationale behind its preemption decisions in this area, the amici States urge the Court to account for at least three features that petitioner's proposed rule does not. *First*, the comprehensiveness of the evidence presented to the FDA. *Second*, whether any additional evidence of the risk came to light after the FDA's decision. And *third*, whether the company's proposed label would have satisfied the state law duty to warn in the first instance. If the company has not presented the full scope of available evidence to the agency; if material evidence post-dating the FDA's decision exists; or if the proposed label change would not have satisfied the

relevant state duty, the defendant should not be able to avail itself of impossibility preemption.

2. A theory of "impossibility" preemption that is unmoored from actual impossibility is nothing more than obstacle preemption masquerading as impossibility preemption. Any such approach cannot be reconciled with the history of drug regulation or basic principles of statutory construction, separation of powers, and federalism. It likewise cannot be reconciled with this Court's conclusion in *Wyeth* that "common-law claims do not stand as an obstacle to the accomplishment of Congress' purposes in the FDCA." 555 U.S. at 581.[5]

Obstacle preemption requires courts to go beyond the text of a statute to determine the broader intent (or intents) behind the enactment. But Congress knows how to express its intent: in the text of the laws it drafts and enacts. Where, as here, it fails to express an intent to preempt state law, this Court should be wary of implying that intent in a vacuum.

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[5] See also Brief of Amici Curiae Vermont, Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Minnesota, Mississippi, Missouri, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Utah, West Virginia, Virginia, Washington, Wisconsin, and Wyoming in Support of Respondent, *Wyeth* v. *Levine*, 555 U.S. 555 (2009) (discussing the problems associated with implied obstacle preemption).

Implied obstacle preemption of this kind mires courts in policy-laden quests for overarching, unstated legislative purposes. See *Williamson* v. *Mazda Motor of Am., Inc.*, 562 U.S. 323, 340 (2011) (Thomas, J., concurring in the judgment) (describing "purposes-and-objectives pre-emption as inconsistent with the Constitution because it turns entirely on extratextual 'judicial suppositions' "). This task is made all the more difficult by the fact that Congress does not preempt any and all state laws that might somehow "frustrate" achievement of one of its objectives.

For example, even if *one* goal of Congress might be to "foster[] uniformity in . . . regulations," that objective may not be "unyielding." *Sprietsma* v. *Mercury Marine*, 537 U.S. 51, 70 (2002). A state tort action that frustrates the goal of uniformity might advance legislators' expectation that injured consumers have access to remedies. *Id.* at 64 (state tort actions, "unlike most administrative and legislative regulations[,] necessarily perform an important remedial role in compensating accident victims"). Congress also might conclude that state tort liability provides a necessary supplement to a regulatory regime.[6] Or an enacted law might simply reflect a compromise among legislators balancing the benefits of stricter federal standards

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[6] See Aaron Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 297 JAMA 308, 310 (2007) (noting that state tort liability can "spur[ ] change in regulatory or corporate procedures, as well as extend[ ] knowledge about drug risks by adding to the evidence available for evaluation by physicians, patients, and regulators"); see also *Bates*, 544 U.S. at 451 ("tort suits can serve as a catalyst" to improve industry and federal regulatory practices).

against the dangers of displacing state tort actions. See *Landgraf* v. *USI Film Prods.*, 511 U.S. 244, 286 (1994) ("Statutes are seldom crafted to pursue a single goal, and compromises necessary to their enactment may require adopting means other than those that would most effectively pursue the main goal.").

Given the difficulty inherent in this task, many members of the Court have expressed concern with the potential scope of this brand of conflict preemption. See *Bates*, 544 U.S. at 459 (Thomas, J., joined by Scalia, J., concurring in the judgment in part and dissenting in part) (approving "th[e] Court's increasing reluctance to expand federal statutes beyond their terms through doctrines of implied pre-emption"); *Geier* v. *American Honda Motor Co., Inc.*, 529 U.S. 861, 907 (2000) (Stevens, J., joined by Souter, Thomas, and Ginsburg, JJ., dissenting) (discussing the importance of "prevent[ing] federal judges from running amok with our potentially boundless (and perhaps inadequately considered) doctrine of implied conflict pre-emption based on frustration of purposes"); *Gade*, 505 U.S. at 111 (Kennedy, J., concurring in part, concurring in judgment) ("A free-wheeling judicial inquiry into whether a state statute is in tension with federal objectives would undercut the principle that it is Congress rather than the courts that pre-empts state law.").

Here too, "[i]f Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point during the FDCA's 70–year history." *Wyeth*, 555 U.S. at 574.

* * *

Impossibility preemption is rare, but that is by design. In this context, it should, at minimum, require a company to show that a federal agency has prevented it (or obviously would have prevented it) from acting in compliance with the state law duty to warn. The States urge the Court against any broad expansion of the impossibility exception in *Wyeth*, lest it become the same sort of roving "obstacle" preemption that the Court initially rejected in that case.

CONCLUSION

The judgment of the court of appeals should be affirmed.

Respectfully submitted.

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IN THE
Supreme Court of the United States

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

DORIS ALBRECHT, ET AL.,
Respondents.

On Writ of Certiorari
to the United States Court of Appeals
for the Third Circuit

BRIEF OF TORT LAW PROFESSORS JOHN C. P. GOLDBERG AND BENJAMIN C. ZIPURSKY AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICI CURIAE*[1]

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Amici have no stake in the outcome of this case other than their academic interest in the rational development of the law. They have serious concerns that the rule proposed by Petitioner in this case, if adopted by the Court, would constitute an intrusion into state tort law that is unnecessary to give full effect to the Supremacy Clause, at odds with basic principles of federalism, and inconsistent with our legal and political traditions, which have always recognized the right of victims of legally recognized, injurious wrongs to an avenue of civil recourse against wrongdoers through state common law.

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[1] Pursuant to Supreme Court Rule 37.6, counsel for *Amici* represent that they (and *Amici*) authored this brief in its entirety and that none of the parties or their counsel, nor any other person or entity other than *Amici* or their counsel, made a monetary contribution intended to fund the preparation or submission of this brief. Pursuant to Rule 37.3(a), counsel for *Amici* also represent that all parties have consented to the filing of this brief.

SUMMARY OF ARGUMENT

Federal preemption of tort law involves the recognition that state common law must give way to federal regulatory law when federal law expressly displaces state law or when there is an actual conflict between them. Yet because, within our federal system, the common law of torts overwhelmingly is the province of the states, this Court has been careful to treat the federal regulatory domain and the state common law domain as largely complementary, not conflicting.

Similarly, this Court has avoided unduly interfering with state tort law even where legitimate constitutional concerns have justified setting certain limits on it, as in the law of defamation and punitive damages. In the area of preemption, this pattern continued in *Wyeth v. Levine*, 555 U.S. 555 (2009), in which the Court found no preemption of failure-to-warn claims involving brand-name drugs. Petitioner now attempts an end-run around *Levine* by arguing that FDA's rejection of Petitioner's proposed label demonstrates that it was "impossible" for Petitioner to give the adequate warnings required to avoid tort liability. Given the absence of any statutory prohibition on Petitioner's ability to issue enhanced warnings of newly discovered medical risks, and given that Petitioner's proposed warning contained deficiencies in the dimensions of adequacy that state law deems significant (deficiencies that FDA also recognized in its rejection), the Court should not credit this argument. Indeed, it cannot do so without adopting an unstructured, expansive notion of "impossibility" that would efface the line between legitimately ensuring that state tort law operates within constitutional confines and illegitimately undertaking to fashion a general common law of failure-to-warn liability.

An examination of failure-to-warn law for prescription drugs reveals that Petitioner is asking the Court for an unnecessary and inappropriate displacement of state law. Whether a warning is adequate involves considerations such as the nature and magnitude of the risk and the clarity and communication of the warning. The warning proposed by Petitioner was almost certainly not adequate as a matter of law, and in any event posed a fact issue for resolution at trial. FDA's rejection of Petitioner's understated and muddled warning in no way indicates that the agency would have rejected a warning of the risk of atypical femoral fractures that was adequate in the relevant dimensions. Indeed, FDA's rejection of a proposed warning in *Levine* (which this Court found had no preemptive effect) was considerably stronger than the proposal rejected by FDA in this case, thus underscoring the insufficiency of Petitioner's showing. There is no indication in this case that FDA's "rejection" foreclosed an attempt to add a warning that would be adequate under state law. In short, it was entirely possible for Petitioner to comply with both federal and state law by simply proposing or adding an adequate warning.

Finally, Petitioner's dire prediction that, without further federal court oversight, state law will thwart federal regulations by allowing juries to run wild is simply overblown. Insofar as juries hearing failure-to-warn claims against Petitioner will be required to answer a "counterfactual" question about whether FDA would have approved an adequate warning, this is the sort of thing juries are entrusted to do every day. Moreover, they do it in a context that has significant, existing protections to ensure proper deference to prescribing physicians' expertise and appropriate

judgments by FDA, and to ensure the reliability of the scientific evidence presented to them. The learned intermediary rule, the defense of regulatory compliance, and trial judges' screening of proposed expert testimony are robust protections against overreach. These and other checks built into the operation of state tort law are more than sufficient to negate any need for further federal court oversight.

ARGUMENT

I. RESPECT FOR STATE TORT LAW REQUIRES A RESTRAINED APPROACH TO IMPLIED PREEMPTION ANALYSIS

Petitioner, the manufacturer of a brand-name prescription drug, seeks to persuade this Court that it deserves to win failure-to-warn claims brought against it without any determination as to the adequacy of the warnings it issued. It claims that the doctrine of "impossibility" preemption allows for such a result. However, unlike defendants who raise *express* preemption arguments, as well as those who raise implied preemption arguments that turn on clear statutory text – *see PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011) (Hatch-Waxman Act's prohibition on unilateral label changes by generic drug manufacturers makes it impossible for them to comply with conflicting state-law requirements) – Petitioner's implied preemption argument has no statutory anchor whatsoever. If the Court accepts Petitioner's invitation to craft an impossibility- based escape-hatch from state tort liability, it will be cutting too deeply into state tort law without a sufficient federal basis.

The application of implied preemption doctrine untethered from any guiding text carries a great risk of undermining federalism values. That is the principal

reason for submitting this *Amicus* brief. With no text to control the determination of federal preemption in this case, the degree to which state common law remains available to provide redress to victims of injurious misconduct depends entirely on this Court and lower federal courts exercising self-restraint.

This brief does not challenge the federal courts' authority to engage in implied preemption analysis. It does, however, point out that the approach to implied preemption that would be necessary for the Court to rule for Petitioner in this case presupposes a conception of that authority that is inconsistent with its role within a federalist system. Crafting the rules that federal judges prefer, rather than applying the common law of the state, would mark a return to the days of *Swift v. Tyson*, 41 U.S. (16 Pet.) 1 (1842). Basic principles of federalism and *Erie Railroad Co. v. Tompkins*, 304 U.S. 64 (1938), call for great caution.

This is not the first time that state common law has been imperiled by tort litigation that found its way to the Supreme Court. Constitutional attacks on defamation law and punitive damages awards have cut deeply into these areas of state law – sometimes too deeply, as has been observed by many Justices, including Chief Justice Rehnquist, as well as Justices Ginsburg, Scalia, Thomas, and White. In those areas – following *New York Times Co. v. Sullivan*, 376 U.S. 254 (1964), and *BMW of North America, Inc. v. Gore*, 517 U.S. 559 (1996) (respectively) – the Court eventually chose to reject aggressive construction of pro-defendant constitutional protection in order to remain true to its federalist commitments. That is what it should do here, too.

A few examples will illustrate the present point. *New York Times Co. v. Sullivan* remains emblematic

of the Court's power and obligation to ensure tort law operates within constitutional boundaries. The advertisement at issue in *Sullivan* did not mention any individual official, yet the plaintiff, a city commissioner, brought suit and won a huge punitive damages verdict. In these circumstances, the Court looked past the form of the litigation and identified it for what it really was – a seditious libel prosecution. It rightly shielded the New York Times from tort liability under the First Amendment.

Sullivan's progeny tell a different story. Media defendants pressed for "elaboration" of *Sullivan*'s holding. The Court soon articulated a sprawling constitutional jurisprudence. In the eyes of some Justices, the Court's burgeoning case law threatened to run afoul of *Erie* and its federalist underpinnings. Most notably, in *Gertz v. Robert Welch, Inc.*, 418 U.S. 323 (1974), Justice White penned an impassioned dissent, arguing that the Court was experiencing substantial mission creep:

> For some 200 years – from the very founding of the Nation – the law of defamation and right of the ordinary citizen to recover for false publication injurious to his reputation have been almost exclusively the business of state courts and legislatures. . . .
>
> But now, using [the First] Amendment as the chosen instrument, the Court, in a few printed pages, has federalized major aspects of libel law by declaring unconstitutional in important respects the prevailing defamation law in all or most of the 50 States.

Id. at 369-70 (White, J., dissenting).

Regardless of whether one agrees with Justice White that *Gertz* would have been the right moment to stem the expansion of federal defamation law, he was surely right to sound a cautionary note. His warning was eventually heeded. Sixteen years after *Gertz*, media defendants asked the Court to hold that the First Amendment precluded tort liability for anything that could be characterized as a statement of opinion. It declined. Writing for a 7-2 majority in *Milkovich v. Lorain Journal Co.*, 497 U.S. 1, 20-21 (1990), Chief Justice Rehnquist recognized that there was already opinion protection within state common law, that powerful First Amendment liability limits had already been crafted by the Court, and that the analytical case for a new and broad additional federal-law shield simply did not hold up to scrutiny. The Court had done enough to ensure that state defamation law operated with proper respect for rights of free speech; doing more would threaten to efface the line between constitutional law and general common law.

A similar pattern has unfolded in the constitutional law of punitive damages, in which federalist concerns have been flagged from the start. In *BMW of North America, Inc. v. Gore*, the majority identified a "notice" problem with a $2 million punishment for nondisclosure of an invisible flaw in the paint of a luxury car. 517 U.S. at 574. In their dissents, Justice Scalia and Justice Ginsburg contended that the Court had allowed the anomalousness of the punitive damages claim in that particular case to spawn an analytically unsound doctrine that cut unduly into state common law. *See id.* at 605 (Scalia, J., joined by Thomas, J., dissenting); *id.* at 612 (Ginsburg, J., joined by Rehnquist, C.J., dissenting).

The defense victory in *Gore* gave litigants an incentive to press to federalize state punitive damages law. A majority of the Justices continued to respond, with the high-water mark being set by *State Farm Mutual Automobile Insurance Co. v. Campbell*, 538 U.S. 408 (2003), which once again garnered dissenting opinions. *See id.* at 429 (Scalia, J., dissenting); *id.* at 429-30 (Thomas, J., dissenting); *id.* at 430 (Ginsburg, J., dissenting). In the years following *Campbell*, the Court received numerous certiorari petitions encouraging it to set a hard-and-fast numeric ratio of punitive to compensatory damages, even in cases involving wrongful death or massive environmental harm.

In part through denial of petitions, the Roberts Court halted the development of constitutional-excessiveness doctrine in punitive damages law. In *Exxon Shipping Co. v. Baker*, 554 U.S. 471 (2008), the Court denied Exxon's certiorari petition on constitutional excessiveness, *Exxon Shipping Co. v. Baker*, 552 U.S. 989 (2007) (mem.) (granting certiorari only on other issues in the case), and used its unquestioned authority in federal maritime law to decide the case on other grounds. In *Phillip Morris USA Inc. v. Williams*, 556 U.S. 178 (2009), the Court repeatedly declined to address the constitutional-excessiveness issue and ultimately permitted a very large Oregon punitive damages verdict to stand. In light of the dissenting opinions over the years of Justices Thomas and Ginsburg (and the clear choice of Justice Breyer to utilize procedural, not substantive excessiveness, concepts), the halting of constitutional-excessiveness decisions can be seen as a deliberate, federalist-inspired effort to respect state tort law through restraint and analytical rigor.

Preemption law presents parallel issues of restraint, as the various Justices' opinions on preemption vividly display. The font of modern preemption jurisprudence as it relates to tort law is an express preemption case rather than an implied preemption case. In *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504 (1992), a majority of the Justices concluded that Congress's adoption of highly specific statutory warnings for cigarettes preempted state failure-to-warn claims, but not other claims, including for fraud. Ever since, members of the Court have articulated worries that defense arguments have sometimes succeeded when restraint and respect for state tort law might have been the better path.

From a (concededly academic) perspective, *Wyeth v. Levine*, 555 U.S. 555 (2009), can be seen as having drawn a line in the sand based on recognition of post-*Erie* limits on the federal courts' lawmaking authority. Even though of course interpreting a different constitutional provision, the Court's *Levine* ruling resembled its refusal to constitutionalize opinion protection in *Milkovich* and its resistance to fixing rigid rules for constitutional excessiveness in *Williams* and *Exxon*. Preemption of all failure-to-warn claims for FDA-approved drugs was for drug manufacturers the brass ring, but six Justices decided that close analysis of the statutory and regulatory framework did not justify the ruling Wyeth sought. Moreover, as Justice Thomas observed in his concurrence, an expansive implied preemption doctrine threatened to undercut the authority of the states to fashion rules of tort law. Although Justice Thomas concluded two years later in *Mensing* that impossibility preemption applies to claims against *generic* drug manufacturers, that result was driven by the clear language of the Hatch-Waxman Act and

the absence of a counterpart in it to the CBE provision relied upon in *Levine*.

In its briefs before the Court in this case, Petitioner is taking another shot at eliminating a broad range of failure-to-warn claims against manufacturers of brand-name drugs, hoping that what the Court was unwilling to do in *Levine* it might do today in a slightly different form. But the Court was right to reject impossibility preemption in *Levine* because it would have undermined the states' traditional power to provide redress to those who can prove their common law claims. Having shown restraint a decade ago to preserve this domain of state sovereignty and individual rights, the Court should not reverse course now, on what is (as Respondents' brief and the discussion below show) a much weaker set of facts.

Unfortunately, Petitioner's brief does not provide the Court with a basic model of the workings of the state failure-to-warn law that it would be displacing were it to find preemption. It similarly overlooks the range of doctrinal and statutory resources that state tort law currently supplies to prescription drug manufacturers to protect them from unwarranted liability and litigation. Parts II and III, *infra*, aim to plug these gaps.

II. PETITIONER'S PREEMPTION ARGUMENT WOULD REQUIRE THIS COURT TO INTERFERE UNDULY WITH A CORE AREA OF STATE TORT LAW

Understanding failure-to-warn law in the pharmaceutical context is a necessary prelude to analyzing Petitioner's preemption argument. When one does so, however, the weakness of that argument becomes evident.

A. Failure-To-Warn Law Provides the Primary Line of Defense Against Unduly Dangerous Prescription Drugs by Requiring Manufacturers To Warn Adequately of Dangerous Side-Effects

Redressing injuries caused by improperly labeled medicines has long been a central concern of state tort law. Indeed, the landmark decision of *Thomas v. Winchester*, 6 N.Y. 397 (1852), was such a case. *Thomas* in turn set the stage for then-Judge Cardozo's decision in *MacPherson v. Buick Motor Co.*, 111 N.E. 1050 (N.Y. 1916), which is widely regarded as the font of modern products liability law. Requiring commercial sellers of drugs properly to warn of their products' hidden dangers is and has always been central to state tort law.

Modern products liability law focuses on whether a product that has injured a consumer left the seller's hands in a defective condition because of a design defect, a manufacturing defect, or a failure to warn. Because products often cannot be designed in a way that eliminates their dangers without destroying their benefits, in many cases what determines whether a product is unduly dangerous are the warnings and instructions that accompany it. Just as they count on manufacturers to adopt non-defective designs, product users justifiably rely on manufacturers to provide adequate warnings. And just as design-defect law requires manufacturers to refrain from adopting unreasonably dangerous designs, so too failure-to-warn law requires them to provide clear, comprehensive, accurate information that is not encumbered by distractions or confusions, and that is presented with sufficient urgency and prominence. In the language of state tort law, manufacturers are required to

provide *adequate* warnings about their products' dangers.[2]

For two reasons – one of principle, and one of policy – the provision of adequate warnings is an especially important issue in the prescription drug context. First, as a matter of principle, because pharmaceuticals are typically administered in connection with medical treatment, this area of a failure-to-warn law bears a close resemblance to the "informed consent" branch of medical malpractice law. *See Canterbury v. Spence*, 464 F.2d 772, 780 & n.15 (D.C. Cir. 1972). The ingestion of a drug implicates one's right to control what goes into one's body. Yet, the invasiveness that comes with the use of drugs is, of course, what renders them immensely valuable. The law of informed consent, which addresses the same invasiveness/health tradeoff in the context of decisions to undergo surgeries and other medical procedures, squares this circle by requiring physicians to make full disclosure of material information and by having judges and juries scrutinize these disclosures carefully. Likewise, in failure-to-warn law as applied to prescription drugs, adequacy of disclosure is crucial to ensuring that drug

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[2] Some states recognize failure-to-warn claims that sound in negligence rather than strict products liability. The differences, if any, between the two causes of action are for most purposes modest. When suit is brought for negligent failure-to-warn, the same adequacy issue arises, though here it is framed as the question of whether the defendant failed to provide the warnings and information that a reasonably prudent manufacturer would have provided. *See, e.g., Winter v. Novartis Pharm. Corp.*, 882 F. Supp. 2d 1113, 1117-18 (W.D. Mo. 2012) (describing the standard for adequate warning under Missouri negligent failure-to-warn law), *aff'd*, 739 F.3d 405 (8th Cir. 2014). Accordingly, this brief will treat strict products liability and negligent failure-to-warn claims interchangeably.

users gain access to valuable products, but on terms that duly protect their bodily integrity and safety.

Second, courts have long appreciated that design-defect law fits pharmaceutical products awkwardly. This is not only because the dangers of many drugs, like their potential benefits, are substantial. It is also because the health risks of a drug may outweigh the benefits for some subset of consumers even though there is another subset of consumers for whom the benefits outweigh the risks. Liability for design defect for pharmaceutical products – if it leads manufacturers to take certain products off the market – thus poses the risk that a minority of consumers who would greatly benefit from a drug lose access to it because some other group of consumers would not benefit from it. The rational policy solution to which the common law has largely converged is to diminish design-defect liability for prescription drugs while keeping failure-to-warn liability in place. *See, e.g.*, RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 6(c) (1998) (adopting a special and highly restrictive test for design defect for prescription drugs, under which a drug is defectively designed only if a reasonable health-care provider, knowing of a drug's foreseeable risks and benefits, would not prescribe the drug for *any* class of patients). These same considerations make it all the more important that drug manufacturers provide adequate warnings and information about their products. The primary way in which tort law promotes drug safety is by requiring manufacturers to provide adequate information of the risks posed by their drugs.[3]

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[3] The learned intermediary rule that applies to failure-to-warn claims concerning prescription drugs in no way diminishes

As noted, a failure-to-warn case turns fundamentally on whether the product in question lacked "adequate" warnings and thereby was rendered unduly dangerous. Under state law, adequacy is a function of the accuracy and completeness of the information accompanying a product, as well as the prominence, clarity, and urgency with which that information is presented. Although there is some variation in how different states have defined adequacy (which is part of why federalism *is* truly in play in this case), the variation is not vast.

In their products liability law treatise, Professors Owen and Davis summarize the relevant principles as applied to prescription drugs in particular:

> The principles of adequacy applicable to warnings generally . . . apply to prescription pharmaceuticals. All material information on possible risks must be conveyed to the relevant medical care provider and be comprehensible to the specialist as well as the general practitioner. The sufficiency of the seller's discharge of its informational obligation is measured in terms of whether the cautionary information conveys the nature, the scope, and the severity

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the importance of adequate warnings. Prescription drugs reach the consumer through his or her treating physician. By requiring a drug company to directly warn only the treating physician, the learned intermediary rule shifts the target of the warning from a consumer, who might lack the knowledge and the appreciation of context necessary to interpret it, to the physician, who is presumed to have both. Simply put, doctors have the professional expertise and responsibility to read, absorb, and convey warnings, and they face legal liability for not doing so. That physicians are expected to take manufacturers' warnings very seriously in informing, advising, and treating their patients makes "adequacy" more important, not less so.

> of the risk, together with a plain statement of how the user may avoid such risks and safely use the product.

2 DAVID G. OWEN & MARY J. DAVIS, OWEN & DAVIS ON PRODUCTS LIABILITY § 19:14 (4th ed. May 2018 Update) ("OWEN & DAVIS") (footnote omitted).

A bare mention of a general class of risks associated with a prescription drug does not satisfy the requirement of adequacy. Instead, a drug's warning must accurately and clearly describe the conditions under which the relevant risks might be realized, the precise complications that might result from the realization of such risks, and the consequences for patients of a failure to heed the warning. Moreover, this information must be communicated in a manner that is likely to alert a reasonably prudent prescribing physician to the danger. As the Ohio Supreme Court has explained:

> The fact finder may find a warning to be unreasonable, hence inadequate, in its factual content, its expression of the facts, or the method or form in which it is conveyed. The adequacy of such warnings is measured not only by what is stated, but also by the manner in which it is stated. A reasonable warning not only conveys a fair indication of the nature of the dangers involved, but also warns with the degree of intensity demanded by the nature of the risk. A warning may be found to be unreasonable in that it was unduly delayed, reluctant in tone or lacking in a sense of urgency.

Seley v. G.D. Searle & Co., 423 N.E.2d 831, 837 (Ohio 1981) (citation omitted). As the previous citation indicates, the adequacy question is usually for the

jury. *Id.* *See also* OWEN & DAVIS § 19:14 (question of adequacy is for the finder of fact).

Whatever the precise standard of adequacy applied in a given jurisdiction, it is abundantly clear that a drug manufacturer's mere mention of its product's dangers (on a product label or in a package insert) is insufficient to satisfy state tort law and avoid liability. Indeed, examples abound of instances in which manufacturers have faced liability for warnings that, while mentioning the relevant health risk, did so in a way that *inadequately* warned of the risk. *See, e.g.*, *Benedi v. McNeil-P.P.C., Inc.*, 66 F.3d 1378, 1387 (4th Cir. 1995) (applying Virginia law) (jury issue presented on whether manufacturer was required to warn of health risks from use of acetaminophen in combination with alcohol); *Guenther v. Novartis Pharm. Corp.*, 990 F. Supp. 2d 1299, 1303-06 (M.D. Fla. 2014) (applying Florida law and affirming a jury finding of liability in a failure-to-warn case alleging injuries caused by bisphosphonate); *Winter*, 882 F. Supp. 2d at 1117-20 (applying Missouri law and finding sufficient evidence for jury on failure-to-warn negligence case involving bisphosphonate); *Michael v. Warner/Chilcott*, 579 P.2d 183, 187 (N.M. Ct. App. 1978) (pharmaceutical product's warning that product "may damage the kidneys" presents jury issue on adequacy).

B. Petitioner's Proposed Warning to FDA Bears All the Hallmarks of an Inadequate Warning

As explained in detail in Respondents' merits brief, the proposed language submitted by Petitioner to FDA – in the best case – failed to provide a clear articulation of the risk of atypical femoral fracture associated with its drug. Petitioner's proposed language confusingly associated a particular and grave risk

(the risk of atypical femoral fracture) with a distinct and distinctly less grave risk (the risk of minor stress fractures of the sort that are normally cured by rest). In fact, Petitioner's proposed language was even more problematic, for it added that "stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonate." JA707. This statement compounded the false equivalence of atypical femoral fractures and garden-variety stress fractures. The latter typically occur in younger people as a result of athletic activity. C.A.App. 1573. That is not a population that typically suffers from osteoporosis. In asserting that the majority of (garden-variety) stress fractures seen by physicians appear in patients who are not taking bisphosphonate, Petitioner's proposed language further diluted what little information it might otherwise convey about the risk to users of its product of atypical femoral fractures.

Even assuming for purposes of argument that there is a biological link between stress fractures and atypical femoral fractures (making it arguably appropriate to mention both in the same label), the particular way in which Petitioner's proposed label associated these two very different injuries has an obvious potential to distract and confuse. Language that is cluttered, that conflates more serious with less serious risks, that "buries the lede," or that is otherwise prone to misinterpretation is at the very core of the adequacy issue in failure-to-warn litigation. As noted above, the question in such cases often is not whether *any* warning was given, but whether the warning that was given was *adequate*. And it is precisely the characteristics on display in Petitioner's proposed language that would support a finding of inadequacy.

C. FDA's Rejection of a Proposed Label That Merely Mentions a Risk of Injury Cannot Be the Basis for an Implied Preemption Defense Based on "Impossibility"

Petitioner's argument boils down to this: FDA's rejection of a proposed label that plainly could be deemed to provide inadequate warnings under state tort law nonetheless suffices to establish that it would not have approved a clearer, stronger, and more obviously adequate warning. This argument comes in two variants: one is that the mere rejection of a proposed label mentioning the risk suffices to ground impossibility preemption (the "mere rejection" version), and a second is that the rejection of the proposed label provides evidence of further facts, which themselves ground impossibility preemption (the "further facts" version).

As shown below, Petitioner's argument fails whether on the "mere rejection" version or the "further facts" version. Needless to say, Petitioner should not be able to claim its prize of implied preemption by toggling between these two versions, either. In the end, however, the reason neither version works is basically the same: Merck's confusion of atypical femoral fractures with much different and much less serious "stress fractures" rendered its proposed warning the very opposite of what patients and their physicians need from a warning. That is why the warning might well be deemed inadequate by a jury applying the common law of torts; it is also why FDA rejected Merck's warning.

1. *The Mere Fact of FDA's Rejection of Petitioner's Proposed Label Cannot Suffice To Establish Impossibility*

As indicated, Petitioner's proposed label mentioned in an oblique, anything-but-clear manner the risk of atypical femoral fracture associated with the use of Fosamax. FDA rejected this label. There is at least a suggestion from Petitioner and supporting *Amici* that these facts alone suffice to establish impossibility preemption – that FDA's rejection of a proposed drug label that *in some manner mentions* the relevant risk establishes that FDA would have likewise rejected *any attempt* to warn of that risk.

Such a suggestion is obviously untenable. To establish the defense of federal preemption, a defendant in a failure-to-warn case such as this one must prove that it was *impossible* to rectify the deficiencies in its warning under state law because federal law clearly prevented it from doing so. *See Levine*, 555 U.S. at 569. The fact that FDA rejected a warning that a jury would surely be entitled to deem inadequate in no way suggests that the defendant was *unable to issue an adequate warning*, for there is no reason to suppose that federal law rendered Petitioner unable to provide an adequate warning as to the danger of atypical femoral fractures. FDA's rejection of a proposed drug label leaves the manufacturer completely at liberty to propose or add a better warning. A drug manufacturer thus does not establish that it was blocked by federal regulatory law from complying with state failure-to-warn law simply by showing that its proposed warning was rejected. Again: such a showing quite obviously leaves open the possibility that a clearer or more compelling warning – one that

would have been adequate and thus avoided liability – would not have been rejected by FDA.

This version of Petitioner's impossibility argument is practically pernicious, not just conceptually unsound. Were it adopted, prescription drug manufacturers would have available to them a simple formula for avoiding liability for failures to warn about previously unknown or underestimated risks. Essentially, all that they would need to do to enjoy the shield of federal preemption is to propose a tepid and inadequate warning. Not only would the acceptance of this argument thus reward subterfuge, it would result in a severe encroachment onto traditional state tort law without any corresponding benefit to a federal regulatory regime that aims to ensure that prescription drugs are properly labeled.

2. *Defendant Cannot Bear the Burden Set Forth in* Levine *of Showing That a Proposed Label That Contains an Adequate Warning Would Have Been Rejected by FDA*

As just demonstrated, there cannot be impossibility preemption merely on a showing of FDA's rejection of a proposed label that facially mentions the relevant risk. In this context, the impossibility question instead concerns whether it would have been possible for Petitioner to adopt a warning that would be deemed adequate under state tort law and that FDA would not reject. If it would have been possible, then there cannot be impossibility preemption.

As explained in *Mensing*, this Court's prior decision in *Levine* places on the manufacturer the burden of establishing clearly that it would have been barred by FDA from giving an adequate warning: "The Court in [*Levine*] asked what the drug manufacturer could

independently do under federal law, *and in the absence of clear evidence that Wyeth could not have accomplished what state law required of it*, found no pre-emption." 564 U.S. at 624 n.8 (italics added). Only a manufacturer that can clearly establish that FDA would have rejected a proposed *adequate* label stands to obtain the protection afforded by the demanding defense of impossibility preemption. A manufacturer whose proposed warning is rejected for other reasons *can* "accomplish[] what state law require[s] of it" by providing an adequate warning, and can do so "independently." *Id.*

As Respondents' brief establishes, this is the very position Petitioner was in. Contrary to Petitioner's contention, FDA's plain language in its rejection of the proposal concerned the running-together of atypical femoral fractures and ordinary stress fractures, not whether there was a scientific basis to justify some strengthening of the existing warning of the association between atypical femoral fractures and long-term bisphosphonate use.

The Court's analysis of the record in *Levine* itself highlights the weakness of this variant of Petitioner's implied preemption argument. Diana Levine lost her arm when an IV-push injection of Phenergan entered her artery. *Levine*, 555 U.S. at 559. She claimed that the labeling of Phenergan inadequately warned of the risks of IV-push administration as opposed to the use of IV-drip or some other method. *Id.* at 564-65. Justice Alito's dissenting opinion reviewed in detail the relevant FDA-approved label, noting that FDA had expressly considered whether to prohibit IV-push as a method of administration but had not done so, and had instead approved warnings with respect to that method of administration. *Id.* at 613-17 (Alito,

J., dissenting). Instead, the label warned that "**INADVERTENT INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY.**" *Id.* at 618. According to Justice Alito, it was thus "demonstrably untrue" that, in 2000 (when Phenergan was administered to Levine), its "labeling did not contain a specific warning about the risks of IV-push administration." *Id.* at 619.

The majority and dissent parted ways concerning what had happened 12 years earlier, in 1988. They agreed that Wyeth had proposed "different language for Phenergan's warning about intra-arterial injection" and that FDA had rejected the proposal. *Id.* at 572 n.5 (majority); *id.* at 605 n.1 (Alito, J., dissenting). The dissent emphasized plaintiff's admission that the 1988 proposal would have prevented Ms. Levine's injury by requiring the IV-drip method, rather than allowing IV-push administration, and argued, therefore, that Wyeth "*did* propose an adequate warning." *Id.* at 605 n.1 (Alito, J., dissenting). By contrast, the majority acknowledged the plaintiff's admission, but relied on findings that the proposed warning was not substantively different than the existing warning in holding that this situation did not result in a preemptive conflict. *Id.* at 572 n.5.

It is undisputed that, for Phenergan, Wyeth had proposed an added warning addressing the exact risk at issue and that FDA had rejected the proposed warning. Although the majority and dissent disagreed as to whether the proposed warning was substantively different from the existing warning, six members of this Court found that FDA's rejection of a proposed warning addressing the same method of administration that injured Ms. Levine failed to provide a sufficient basis on which to displace state failure-to-

warn law. This was much "clearer evidence" of a preemptive regulatory act than FDA's rejection of Wyeth's proposed warning with respect to Fosamax. The *Levine* Court obviously understood that the issue was not whether there was a proposal and rejection of a warning that facially concerned the relevant risk – indisputably, there was – but whether the proposed warning that FDA rejected was *adequate*. *Id.* at 572 ("[Wyeth] does not argue that it attempted to give the kind of warning required by the Vermont jury but was prohibited from doing so by the FDA."). Evidence of a rejection of an *adequate warning* is the "clear evidence" that was missing in *Levine*, *id.* at 571-72, and is likewise missing in the case at bar.

The actual proposal and rejection in *Levine* removed that case from the "hypothetical" or "counterfactual" realm. *See Mensing*, 564 U.S. at 624 n.8. Furthermore, the warning that FDA rejected in *Levine* was quite obviously *stronger* than the one Merck proposed regarding the risk of atypical femoral fractures in the case at bar. The irony of Petitioner's current position is apparent. Even though this Court concluded in *Levine* that Wyeth could constitutionally be subject to failure-to-warn liability despite the fact that its proposed warning was actually rejected by FDA, and despite the fact the warning that it did give was comparatively clear and strong, it now asks the Court to immunize it entirely from liability on the basis of the agency's rejection of a considerably less clear and compelling warning.

III. STATES HAVE AMPLE RESOURCES WITHIN TORT LAW TO KEEP FAILURE-TO-WARN TORT LITIGATION IN CHECK

Petitioner paints a picture of a world in which state tort law leaves drug companies unprotected from the whims of uninformed citizen juries. The real world is nothing like that.

A. Counterfactuals

Petitioner and the government claim that a jury should not decide whether the *Levine* exception was met because that exception presents a question of law. As the Third Circuit recognized, however, this Court's articulation of the exception indicates that it is a question of fact. *See Levine*, 555 U.S. at 571. Of course, Petitioner might mean "question of law" in a conclusory way; they might mean that *juries should not be permitted to* decide whether a defendant has proved that FDA would have rejected a proposed warning (even if it is in essence a question of fact in every particular case). That is presumably why much of Petitioner's brief seems to relate to juries.

Petitioner pours a lot of energy into trying to incite fears of juries. *E.g.*, Pet. Br. 40 (describing "practical nightmare" of permitting multiple juries to use their "'intuitions'"). The fear is inappropriate, given the centrality of the right to jury trial to our legal system, as evidenced by its enshrinement in the federal and state constitutions. U.S. CONST. AMENDS. VI, VII. More to the point, the Federal Food, Drug, and Cosmetic Act itself provides that juries determine whether a drug is "misbranded" based on an inadequate warning. *See* 21 U.S.C. §§ 331(a), 332(b), 334(b), 352(a), (f); *Levine*, 555 U.S. at 570 ("the statute contemplates that federal juries will resolve most misbranding claims"). Juries play an integral role

in the *federal* system, and Congress itself expressed confidence in juries' ability to evaluate warnings on prescription drugs.

Petitioner foments distrust of juries in its repeated use of the term "counterfactual," which appears a whopping 13 times in its brief. The insinuation is that our legal system courts disaster by allowing juries to conduct an inquiry of the form "What would have happened if the defendant had done what the plaintiff contends it should have done, but did not do?" Petitioner's hyperbolic language about "counterfactual quagmires" not only insults the venerable institution of the jury but also displays disregard for basic tort law that is taught each year to 1Ls around the country. Typically – in what many lawyers would regard as a *pro-defendant* treatment of cause-in-fact doctrine when compared to treatments that emphasize the more open-ended language of "substantial factor" – students are taught: (a) *the jury* ordinarily decides the question of cause-in-fact in a negligence or products liability case; (b) cause-in-fact is usually determined by the *but-for* test; and (c) the but-for test requires the jury to decide what would have happened if the defendant had not acted negligently or had not sold a defective product. On this traditional approach, *a counterfactual question* lies at the very heart of the jury's role. It is emblematic of Petitioner's eagerness for the Court to forget state tort law that it suggests, bizarrely, that juries are incapable of handling questions with which they are routinely entrusted.

Of course, there are limits on the issues that juries should decide. State judges and legislators possess and implement many devices to constrain jury discretion, reflecting the considered judgment of a particular state's government concerning how these cases should proceed. Proper determination of the

question of fact comes only after proper instruction on the applicable law, as well as vetting to ensure that submission of the question is proper in the first instance. This is a basic principle of state law as well as federal law. *See, e.g., CSX Transp., Inc. v. McBride*, 564 U.S. 685, 704 (2011) ("Properly instructed on negligence and causation, and told, as is standard practice in FELA cases, to use their 'common sense' in reviewing the evidence, juries would have no warrant to award damages in far out 'but for' scenarios. Indeed, judges would have no warrant to submit such cases to the jury.") (citation omitted). There are also myriad protections to ensure that only appropriate questions reach the jury in the first instance.

B. State Tort Law Provides Multiple Layers of Protection To Respect Federal Regulation and To Prevent Jury Determination of Unwarranted Questions

Defendants in failure-to-warn cases enjoy the same general protections available in other suits. For example, this Court established heightened pleading requirements in *Bell Atlantic Corp. v. Twombly*, 550 U.S. 544 (2007), and *Ashcroft v. Iqbal*, 556 U.S. 662 (2009). These requirements certainly apply to federal courts sitting in diversity and can lead to dismissal on the pleadings. *See, e.g., Anderson v. Abbott Labs.*, No. 3:11-CV-1825-L, 2012 WL 4512484 (N.D. Tex. Sept. 30, 2012) (dismissing claims of failure to warn of the association between the rheumatoid arthritis drug Humira and pediatric leukemia). Claims in which there are no genuine issues of material fact are subject to summary judgment. And courts can correct error post-trial with motions for judgment as a matter of law, motions for new trial, and appeals. In addition to such general protections, however, states have put in place three targeted protections for failure-to-

warn cases that respect the prescribing physician's expertise, defer to appropriate judgments by FDA, and guard scientific integrity.

1. *Prescribing Physician/Learned Intermediary*

Failure-to-warn cases involving prescription drugs have a unique feature that enables juries to assess with considerable reliability the existence and causal significance of an omitted adequate warning. Barring some extraordinary circumstance, there will be sworn testimony, either live or by deposition, of the prescribing physician. This provides an actual look at how a particular warning functioned in the real world.

For many decades, the overwhelming majority of state courts have applied the "learned intermediary doctrine" in prescription drug cases. They have held fast to this rule even in the face of criticism and a few prominent decisions questioning it. According to this doctrine, a drug company generally has no duty to warn a patient directly, but can discharge its duty by giving an adequate warning to the physician. The products liability provisions of the Third Restatement of Torts summarize the doctrine as follows:

> (d) A prescription drug or medical device is not reasonably safe due to inadequate instructions or warnings if reasonable instructions or warnings regarding foreseeable risks of harm are not provided to:
>
> > (1) prescribing and other health-care providers who are in a position to reduce the risks of harm in accordance with the instructions or warnings; or
> >
> > (2) the patient when the manufacturer knows or has reason to know that health-care providers will not be in a position to

> reduce the risks of harm in accordance with the instructions or warnings.

RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 6(d). "The rationale supporting this 'learned intermediary' rule is that only health-care professionals are in a position to understand the significance of the risks involved and to assess the relative advantages and disadvantages of a given form of prescription-based therapy." *Id.*, cmt. b.

The prescribing physician is always a critical witness. His or her testimony gives real-world insight into the adequacy of a warning as interpreted by an actual physician. But this testimony can also end the litigation as a matter of law. Generally, unless the prescribing physician testifies that a different warning would have made a difference – by causing the physician to modify the prescription, to give the patient additional warnings, or not to prescribe the drug at all – the drug company will file a motion for summary judgment based on lack of causation, and some courts will deem such evidence sufficient to justify granting the motion. *See, e.g., In re Avandia Mktg., Sales Practices & Prods. Liab. Litig.*, 639 F. App'x 874, 878 (3d Cir. 2016) ("[s]ummary judgment is properly granted on a failure to warn claim where the record 'is devoid of evidence to support [the] argument that a different warning would have altered [the physician's] prescribing methods'") (citation omitted; first alteration added).

2. *Regulatory Compliance*

Because FDA regulates prescription drugs, virtually every drug company in a failure-to-warn case emphasizes at trial that it operates within a regulated industry; that it cannot distribute a drug until FDA

approves it; and that FDA has approved the drug's label. The Third Restatement of Torts puts forward the principle that, while compliance with safety statutes and regulations is proper for a jury to consider with respect to certain risks, *see* RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 4(b), the "traditional view" is that such regulations "provide only minimum standards." *Id.* § 4 cmt. e ("Thus, most product safety statutes or regulations establish a floor of safety below which product sellers fall only at their peril, but they leave open the question of whether a higher standard of product safety should be applied.").

As is characteristic of our federal system in the domain of torts, however, there is variation among the states, and some have enacted – not without controversy – statutes incorporating a regulatory compliance defense, or giving greater weight to evidence of compliance than is traditionally given under common law rules. *See, e.g.*, ARK. CODE ANN. § 16-116-205; COLO. REV. STAT. § 13-21-403; FLA. STAT. § 768.1256; IND. CODE § 34-20-5-1; KAN. STAT. ANN. § 60-3304(a); MICH. COMP. LAWS § 600.2946(4); N.J. STAT. ANN. § 2A:58C-4; N.D. CENT. CODE § 28-01.3-09; TENN. CODE ANN. § 29-28-104; TEX. CIV. PRAC. & REM. CODE ANN. § 82.007; WASH. REV. CODE § 7.72.050(2). Such statutes reflect a policy choice by these jurisdictions to dampen certain forms of tort liability and litigation. These states' erection of new barriers to tort liability is a further reason that the doctrinal tool Petitioner hopes the Court will create here is neither necessary nor constitutionally appropriate.

3. *Scientific Reliability*

In *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 597 (1993), this Court held that Federal

Rule of Evidence 702 assigns district judges the role of "gatekeep[ers]" who must screen scientific evidence to ensure its reliability. "Post-*Daubert*, the federal district courts, exercising their newly appointed 'gatekeeper' function, have scrutinized expert testimony more closely, often holding rigorous pre-trial '*Daubert* hearings' – that are often outcome determinative – to determine the admissibility of proffered expert testimony." David G. Owen, *A Decade of Daubert*, 80 DENV. U.L. REV. 345, 362 (2002).

The majority of states have now adopted some form of that standard, with the result that almost every failure-to-warn case includes a separate proceeding within the overall litigation to determine scientific reliability and the consequent admissibility of expert testimony. This can be a major hurdle for failure-to-warn plaintiffs. *See, e.g.*, *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig.*, 892 F.3d 624, 632-45 (4th Cir. 2018) (no abuse of discretion in excluding three of plaintiffs' experts under *Daubert*, effectively dismissing more than 3,000 claims); *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 795-800 (3d Cir. 2017) (no abuse of discretion in excluding plaintiffs' expert and granting summary judgment, effectively disposing of 315 claims). Again, recognition of an existing and effective check on liability belies Petitioner's overblown claims about the pressing need for a federal-law immunity from liability.

CONCLUSION

State tort law requires prescription drug manufacturers to provide adequate warnings of their drugs' harmful side-effects. Nothing in federal law prohibits manufacturers from providing such warnings and thus avoiding liability. Nor is there any reason to believe that state courts are administering failure-to-warn law in a way that threatens the sort of interference with federal interests that might justify further federal-court oversight to rein them in. For the past 80 years – since moving from *Swift v. Tyson* to *Erie Railroad Co. v. Tompkins* – this Court has kept out of the business of shaping the precise contours of state tort law. Consistent with this commitment, the Court declined to interfere with state failure-to-warn claims against brand-name drug manufacturers almost a decade ago in *Wyeth v. Levine*. In today's case, Petitioner invites the Court to engage in an untethered form of implied preemption analysis, in effect, asking the Court to abandon the balanced and sensible position it staked out in *Levine*. When the content of state failure-to-warn law is adequately recognized and the defendant-protective resources of today's state tort law are fully appreciated, it becomes apparent that federalizing this area of law is neither necessary nor appropriate.

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No. 17-290

IN THE
Supreme Court of the United States

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

DORIS ALBRECHT, ET AL.,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Third Circuit

BRIEF OF JEROME P. KASSIRER, M.D., MARCIA ANGELL, M.D., and GREGORY CURFMAN, M.D. AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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QUESTION PRESENTED

Whether the Third Circuit correctly denied summary judgment on Petitioner's preemption defense because clear evidence did not demonstrate that the FDA would have rejected a properly worded warning about atypical femoral fractures.

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INTEREST OF *AMICI CURIAE*[1]

Amici curiae are doctors, professors, and former editors of the most prestigious medical journals in the world. They have a keen interest in drug safety.

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[1] Petitioners and Respondents have filed blanket consents to the submission of *amicus* briefs with this Court. No counsel for a party authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amicus curiae* or counsel made a monetary contribution to its preparation or submission.

Gregory Curfman, MD, is Deputy Editor of the Journal of the American Medical Association. Dr. Curfman was previously the editor in chief of Harvard Health Publications, the publishing division of Harvard Medical School, and, prior to assuming this role, had a 28-year career as an editor of the New England Journal of Medicine, most recently as the Journal's Executive Editor. At NEJM, he founded the Perspective section, which focuses on issues at the interface of medicine and society. HHe is a member of the Faculty of Medicine at Harvard Medical School (HMS) and holds an affiliated faculty appointment in the HMS Department of Health Care Policy.

The issue before this Court is one of immense importance from the perspective of public health and safety. *Amici* are familiar with the professional literature relevant to this Court's decision in this case and feel compelled to provide the Court with pertinent studies that bear on the question presented. The matter under review by this Court – whether the tort action is preempted – should be informed by a better understanding of the respective and complimentary roles played by the FDA and by tort litigation. In providing this information, amici ask this Court to affirm the decision of the Court below.

SUMMARY OF ARGUMENT

Pharmaceutical companies usually learn about dangers caused by their drugs long before the Food and Drug Administration (FDA) does, but those companies have not consistently disclosed this

information to the FDA. The records in state tort liability cases document too many instances where drug manufacturers withheld key information from the FDA or willfully chose not to investigate legitimate concern safer drug safety signals arose. Even when disclosed, the information may not be delivered in a timely fashion or its significance is improperly downplayed.

The process of developing appropriate drug safety labeling is inevitably a slow one. Manufacturers will often fight against stricter label warnings, even as they continue to market their problematic drugs to unsuspecting physicians and patients. Full information too often becomes public only when discovery in product liability cases unearths it. State tort law provides essential information-gathering tools through which the health care community obtains safety and effectiveness information about drugs.

Recent developments further highlight the importance of tort liability to the overall system of drug safety. The volume of new drugs seeking FDA approval continues to grow. More and more new drugs obtain approval through expedited development and review processes on the basis of abbreviated testing in clinical trials. These drugs require greater attention after approval to glean important information about associated adverse events and other harms. But the FDA has limited resources to monitor the prevalence or emergence of adverse events after an approved drug hits the market.

The FDA acknowledges that it cannot perform these necessary tasks alone. State tort liability plays a critically important part in that post-approval monitoring process, providing incentives for earlier disclosure by manufacturers and exposing information about risks key risks that might not have been clearly described to the FDA. To protect the drug safety system of which the FDA is only a part, this Court should not curtail patients' ability to bring tort actions about adverse drug events without rigorously clear evidence that the FDA would not have approved the precise warning that is the subject of the lawsuit.

ARGUMENT

Prescription drugs have enormous potential to address the various maladies that afflict the human condition, but also carry risks of adverse reaction and even fatality. The Centers for Disease Control and Prevention (CDC) estimates that "more than 1 million individuals are seen in hospital emergency departments for adverse drug events each year in the United States," with more than one-quarter of these patients requiring hospitalization for further treatment. CDC, *Medication Safety Program: Adverse Drug Event Monitoring*, https://www.cdc.gov/medicationsafety/program_focus_activities.html. One study by CDC researchers showed that four in every 1,000 individuals taking prescription drugs suffered an adverse drug event, which constitutes the most common form of iatrogenic harm in health care. Nadine Shehab, *et al.*, *US Emergency Department Visits for Outpatient*

Adverse Drug Events, 2013-2014, 316 J. Am. Med. Ass'n 2115, 2124, 2116 (Nov. 22/29, 2016).

The Federal Food, Drug, and Cosmetic Act (FDCA), 52 Stat. 1040, *as amended*, 21 U.S.C. § 301 *et seq.*, provides a mechanism for addressing drug safety and seeks "primarily to protect consumers from dangerous products." *United States v. Sullivan*, 332 U.S. 689, 696 (1948). With respect to drugs, the statute addresses patient safety by requiring new drugs to proceed through a regulatory approval process conducted by the Food and Drug Administration (FDA), while operating alongside traditional state tort liability, which, by providing compensation for avoidable injuries, incentivizes drug manufacturers to monitor adverse events and convey accurate warnings. *Wyeth v. Levine*, 555 U.S. 555, 575 (2009).

A key component of the FDA's regulatory scheme is proper labeling of drugs to assure that medical authorities and patients have the information necessary to make informed decisions about the risks associated with taking a prescription drug. *See* FDA, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3922, 3934 (2006). Proper labeling that incorporates adequate warnings seeks to minimize the instances in which physicians prescribe and patients suffer avoidable harms from prescription drugs. Tort liability attaches, for example, when the drug manufacturer fails to warn adequately in its drug's labeling or otherwise about a particular adverse reaction and the plaintiff suffers harm caused by that adverse reaction as a result.

According to the FDA's rules, a drug's labeling "must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." 21 C.F.R. § 201.57. The brand-name manufacturer bears responsibility to update the labeling as needed, which the FDA subsequently reviews.

The tort system plays a critically important role in that system of patient safety. By itself, the FDA lacks the resources and information needed to monitor patient outcomes arising from the drugs it has approved. The agency relies heavily on manufacturers to convey to it reported adverse events, as well as the results of post-approval clinical trials and other studies that the manufacturer has conducted. The manufacturers do not consistently discharge those obligations, sometimes withholding information about adverse events and drug safety concerns expressed by their own researchers. Too often, when they do notify the FDA, the information conveyed is incomplete or reflects the manufacturer's desire to minimize problems to maintain the drug's position in the marketplace.

Time and time again, tort litigation has revealed risks of medical products that the FDA had not known about or that the manufacturers had actively sought to obscure. Tort litigation therefore serves a vital purpose in informing patients, their caregivers, and the FDA about the risks and benefits of medical products. Insofar as this case either reopens the preemption question settled in Wyeth or

contemplates changes to its application that would reduce the viability of tort litigation, it poses grave risks to public health, and impinges on the work of researchers and doctors seeking to improve drug safety.

I. THE FDA LACKS SUFFICIENT INFORMATION AND RESOURCES TO MONITOR PHARMACEUTICAL RISK AND NEEDS THE ASSISTANCE PROVIDED BY TORT LAW.

A. The Number of New Drug Applications (NDAs) Remains High.

In *Wyeth*, this Court recognized that "Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness" because it was "aware[] of the prevalence of state tort litigation" and chose not to enact an express preemption provision. 555 U.S. at 575. It further understood that the "FDA has limited resources" and that "manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge." *Id.* at 578-79.

The task the FDA faces in approving new drugs and monitoring the emergence of new risk continues to grow. An August 2016 industry report, using data from the FDA, found that the agency had approved 478 new prescription medicines since 2000. Genia Long, *The Biopharmaceutical Pipeline: Innovative Therapies in Clinical Development,* at 1-2, available at http://phrma-docs.phrma.org/files/dmfile/Biopharmaceutical-Pipeline-Full-Report.pdf. The new

approvals during that period represented an average of 28 per year. Still, averaging the approval rate masks the increased rate experienced in recent years and the high likelihood that the recent rise in NDAs is the new norm.

The FDA reports that in 2015, 45 new prescription drugs were approved.[2] Although there was a drop in 2016 to 22 new approvals,[3] the number more than doubled in 2017 to 46.[4] As of November 16, 2018, the number of new drug approvals for 2018 have already surpassed every year since 2000 with 49 new drugs approved.[5]

This recent increase in new drug applications and approvals shows no signs of abating. The industry report that track new drug approvals indicates that, as of August 2016, manufacturers had lined up more than 6,300 new drugs that will soon be submitted to the FDA for review, while thousands more are in clinical development. *Biopharmaceutical*

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[2] FDA, Novel Drug Approvals for 2015, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm430302.htm.

[3] FDA, Novel Drug Approvals for 2016, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm483775.htm.

[4] FDA, Novel Drug Approvals for 2017, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm483775.htm.

[5] FDA, Novel Drug Approvals for 2018, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm483775.htm.

Pipeline, at 5. Most investigational drugs that reach the NDA stage receive approval. Leonard V. Sacks *et al.*, *Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000-2012*, 311 J. Am. Med. Ass'n 378, 383 (2014), available at https://jamanetwork.com/journals/jama/fullarticle/1817795 (finding 73.5% of the 302 applications during the study period were approved). The pace of new drug approvals makes reliance upon all means of determining adverse events during the postmarketing phase, including tort litigation, a priority. Tort cases can identify undisclosed risks, illuminate flaws in study design, and identify areas of concern that require further study. These gaps cannot otherwise be filled.

B. Today, Drugs Obtain Approval More Quickly, Relying on Thinner Initial Evidence.

When this Court decided Wyeth, the FDA received more information about medicines in the premarket phase than it receives, on average, today. For that reason, the postmarketing information-gathering role of tort liability is more important than it has ever been. The pressure to approve applications quickly is a constant, resulting in drugs making it to the market with thin initial evidence. A "standard review" generally takes about 10 months, while a priority review, which abbreviates the time to approval, though not the process of approval, takes

six months.[6] Congressional Research Service, R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness,* May 8, 2018, at 7, 9, available at https://fas.org/sgp/crs/misc/R41983.pdf. *See also* 21 U.S. Code § 355(c). In 2016, the median review time was 7.8 months. John K. Jenkins, CDER New Drug Review: 2016 Update, at 20 (Dec. 14, 2016), https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM533192.pdf.

Recent substantial leaps in the speed of FDA review process periods has not stemmed industry complaints, often echoed by public officials, that the amount of data and the length and complexity of clinical trials that are a prerequisite to an NDA still excessively delay the entry of new drugs to market.[7] In late 2016, with industry support, Congress enacted and the president signed Public Law No. 114-255, 130 Stat. 1033 (Dec. 2016), the 21st Century Cures Act, which states that its purpose is to

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[6] The FDA employs several different expedited development and review pathways for drugs deemed to address serious or life-threatening conditions, referred to as "first-in-class" drugs: priority review, accelerated approval, fast track approval, and breakthrough therapy designation. *See, generally,* Erin E. Kepplinger, *FDA's Expedited Approval Mechanisms for New Drug Products,* 34 Biotechnol. Law Rpt. 15 (Feb. 1, 2015), available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4326266/.

[7] *See* Executive Office of the President, President's Council of Advisors on Science and Technology, "Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation" (Sept. 2012), at 14.

"accelerate the discovery, development, and delivery of 21st century cures" by, *inter alia*, reducing the evidence needed to obtain FDA approval of new drugs. The expedited processes for premarket approval enacted in the 21st Century Cures Act puts a further premium on obtaining complete and accurate post-market information and the rapid incorporation of emerging information and appropriate new warnings.

C. Expedited Pathways to Approval Require the FDA to Approve Drugs With Less Safety Evidence than Standard Approvals.

The FDA has available to it four different expedited development and review pathways for investigational drugs: Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review. FDA, Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review, available at https://www.fda.gov/ForPatients/Approvals/Fast/default.htm.

To understand the impact that these pathways and processes have in facilitating the completion of testing and clinical studies in lesser time and with fewer subjects, it is useful to review the information the FDA uses to approve new drugs through the standard process. The FDA receives premarket information from clinical trials that are conducted by the drug manufacturers. While clinical trials represent an important aspect of drug development by providing efficacy assessments, their ability to assess a complete safety profile is inherently limited.

Institute of Med. of the National Academy of Science, *The Future of Drug Safety* (Alina Baciu, *et al.*, eds., 2006), at 38. To demonstrate efficacy, studies generally range between a few hundred to 3000 subjects with a duration of a few weeks to a few years. These studies cannot fully account for: 1) the effects of long-term cumulative dose or latent side effects; 2) rare side effects or those most pronounced in sub-populations; or 3) potential side effects not accounted for in clinical trial designs. In addition, once a drug is used in routine clinical practice, it is often used in patients with multiple co-morbidities excluded from enrolling in trials or taking other medications not permitted for trial participants.

The FDA conducts no independent testing, but must rely upon information provided by the party most interested in bringing the drug to market – the drug manufacturer. That information often presents interpretative challenges. The manufacturer's first-hand knowledge of the data puts the FDA at a disadvantage compared to the company. *See* FDA Science Board Report, *FDA Science and Mission at Risk*, at 31 (2007) <http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%C20and%20Technology.pdf>.

Post-approval evaluation of drug risks has not cured the serious problems that were not identified in the pre-approval process. The FDA has acknowledged that expediting drug application approvals can pose risks for patients. GAO, No. 16-192, *FDA Expedites Many Applications, But Data for Postapproval Oversight Need Improvement*, at 9 (Dec.

2015), available at https://www.gao.gov/assets/680/674183.pdf. Still, an ever-increasing number of drugs are reviewed under one of these expedited programs. *See* pp. 26-36 *supra*. Although intended to apply only to drugs "offering the greatest promise of therapeutic advance to patients with no other reasonable therapeutic choices," they have become the regular process for a growing number of NDAs. Aaron S. Kesselheim *et al.*, *Trends in Utilization of FDA Expedited Drug Development and Approval Programs, 1987-2014: Cohort Study*, 351 Brit. Med. J. h4633, at *2 (Aug. 17, 2015), available at https://www.bmj.com/content/bmj/351/bmj.h4633.full.pdf.

Approximately one-third of approved drugs since 1987 qualified and used one of the expedited approval programs, with the percentage jumping to 65 percent in 2014. Margot Sanger-Katz, "Speedy Drug Approvals Have Become the Rule, Not the Exception," N.Y. Times, May 1, 2015, https://www.nytimes.com/2015/05/02/upshot/speedy-drug-approvals-have-become-the-rule-not-the-exception.html. *See also* Jonathan J. Darrow *et al.*, *Drug Development and FDA Approval, 1938–2013*, 370 N.E.J.M. 2465 (Jun. 26, 2014).

It makes sense that testing in fewer patients, using "surrogate" markers of success (such as cholesterol level) instead of clinical endpoints (such as reduced mortality), and shortening review periods make it more difficult to cull indicators of harm in the data collections contained in an NDA. The reduced length of clinical trials and reviews, as well

as reliance on surrogate endpoints rather than clinical endpoints, correlate with increases in safety events discerned after market approval that have required the approved drugs to be withdrawn or feature a boxed warning.[8] *See* Nicholas S. Downing *et al.*, *Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010*, 317 J. Am. Med. Ass'n 1854 (2017), available at https://jamanetwork.com/journals/jama/fullarticle/2625319; Daniel Carpenter, *et al.*, *Drug-Review Deadlines and Safety Problems*, 358 New Engl. J. Med. 1354 (2008), available at https://www.nejm.org/doi/full/10.1056/NEJMsa070634 1; 2008;358:1354-61; Mary K. Olson, *The Risk We Bear: the Effects of Review Speed and Industry User Fees on New Drug Safety*, 175 J. Health Econ. 175 (2008). One recent matched cohort study of drugs approved over the last two decades found that compared with non-expedited pathway drugs, expedited pathway drugs had a 48% higher rate of post-approval safety-related labeling changes to boxed warnings and contraindications, the two most clinically important categories of safety warnings. Sana R. Mostaghim *et al.*, *Safety Related Label Changes for New Drugs after Approval in the US through Expedited Regulatory Pathways: Retrospective Cohort Study*, 358 Brit. Med. J. j3837

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[8] A black-box warning "appears on a prescription drug's label and is designed to call attention to serious or life-threatening risks." FDA, A Guide to Safety Terms 2 (Nov. 2012), available at https://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM107976.pdf.

(2017), available at https://www.bmj.com/content/358/bmj.j3837.

In sum, developments in the regulatory system in recent years make the tort system still more important as an impetus to transparency and as a strong incentive to encourage companies to disclose adverse events fully to the FDA as rapidly as possible. The higher incidence of safety issues strongly suggests that expedited review forces the FDA to approve NDAs before more preliminary data is available and requires every available tool to expose unknown risks once the drug is in the marketplace. Tort litigation addresses a gap and provides an essential tool in this process.

II. KNOWLEDGE OF RISKS POSED BY NEW PHARMACEUTICALS DEVELOPS EACH YEAR, BUT THE FDA LACKS THE CAPACITY TO REGULATE AND RESPOND EFFECTIVELY.

A. The FDA Has Limited Resources.

The FDA has suffered chronic underfunding, despites its mission to ensure the safety of drugs, medical devices, and food supplies. Institute of Medicine, Challenges for the FDA: The Future of Drug Safety: Workshop Summary 15 (2007). Its budget has increased largely by greater reliance on user fees charged under the Prescription Drug User Fee Act of 1992 (PDUFA), Pub. L. No. 102-571, 106 Stat. 4491. PDUFA originally limited user-fee revenue to apply to review of NDA time to approval,[9]

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[9] The influx of money through PDUFA is credited with effecting a 52 percent reduction in the time to approval for NDAs during

though more recent versions have permitted some use for post-market safety activities. Still, the "spirit of the limitation remains the same," reflecting the motivation for PDUFA from the beginning: reducing NDA time to approval. Patrick O'Leary, *Funding the FDA: Assessing the User Fee Provisions of the FDA Safety and Innovation Act of 2012*, 50 Harv. J. on Legis. 239, 242-43 (2013). With ever-increasing dependence on user fees,[10] PDUFA has had the "unintended but pernicious consequence of shrinking the relative funding available for non-review activities such as enforcement" and post-approval drug safety oversight by the FDA. *Id.*

Little has changed since Kesselheim and Avorn concluded that "clinical trials and routine regulatory oversight as currently practiced often fail to uncover important adverse effects for widely marketed products." Aaron S. Kesselheim & Jerry Avorn, *The*

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the statute's first five years. Cassie Frank *et al.*, *Era of Faster FDA Drug Approval Has Also Seen Increased Black-Box Warnings and Market Withdrawals*, 33 Health Aff. 1453, 1453 (Aug. 2014).

[10] User fees constituted thirty-five percent of the FDA's total FY 2012 budget, and every subsequent budget proposal has asked the FDA to increase that dependence. O'Leary, 50 Harv. J. on Legis. at 249-50. For example, the FY2018 budget proposed a $1.3 billion increase in user fees to fund the FDA. Robert Atlas and Timothy J Murphy, *Opinion: Five key takeaways from Trump's budget proposal*, Managed Healthcare Executive (Jun. 18, 2017), available at http://www.managedhealthcareexecutive.com/healthcare-reform/opinion-five-key-takeaways-trumps-budget-proposal.

Role of Litigation in Defining Drug Risks, 297 J. Am. Med. Ass'n 308, 311 (2007).

Even if information produced by postmarket clinical trials were more perfect, the task of reviewing those results and synthesizing it with other medical knowledge is daunting. As one group of researchers observed, "the task keeps increasing in size and complexity." Hilda Bastian *et al.*, *Seventy-Five Trials and Eleven Systematic Reviews a Day: How Will We Ever Keep Up?*, PLoS Med 7(9): e1000326 (2010), available at https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000326.

Because the regulatory scheme relies so heavily on manufacturers to undertake the post-marketing review and formulate changes to the label, in part, due to the resource imbalance between the FDA and the applicant for approval, it is entirely natural for the FDA to reject an inadequate and misdirected warning and suggest the manufacturer come back with a more appropriate one, rather than develop one on the FDA's own. After all, it is the manufacturer that conducted the research, and the FDA only had second-hand knowledge of its meaning. Still, as the tort system has shown by exposing internal documents obtained through discovery, manufacturers do not always share the misgivings and findings of their researchers with the FDA, and that litigation is the only way to obtain research hidden from the agency and the public.

B. The FDA Has Limited Access to Relevant Data.

The entire process of NDA approval and postmarket monitoring depends on the drug's manufacturers to conduct the clinical trials, monitor adverse events, and propose all labeling changes. *Wyeth*, 555 U.S. at 571. That dependency does not change once the FDA approves a drug for the market. In 2007, Congress enacted the Food and Drug Administration Amendments Act (FDAAA), Pub. L. No. 110-85, 121 Stat. 823, which gave the FDA authority to order pharmaceutical companies to conduct drug safety studies after a drug has received approval and is on the market. 21 U.S.C. § 355(o)(3). However, the enforcement mechanism is cumbersome to implement and results in relatively small monetary penalties; in fact, in the decade since FDAAA was enacted, despite ongoing reports of delayed or non-initiated postmarket study commitments, the FDA has not imposed such fines. Holly Lynch, It's Time to Levy Penalties for Failing to Report Clinical Trial Results, STAT, https://www.statnews.com/2018/01/17/time-levy-penalties-failing-report-clinical-trial-results/.

However, even the prospect that post-approval trials might be conducted does not fully ensure that all possible safety-related information will be acquired via this process. In particular, clinical trials may not be able to uncover risks that are rare, revealed over significant periods of time, or adversely affect specific segments of the population not enrolled in the trial. A recent study found that NDA holders frequently fail to meet their post-marketing

commitments and requirements. Steven Woloshin *et al.*, *The Fate of FDA Postapproval Studies*, 377 N. Engl. J. Med. 1114 (Sept. 21, 2017), available at https://www.nejm.org/doi/full/10.1056/NEJMp1705800?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed. Because post-marketing studies are not ensuring a flow of information on harms to the FDA, the discovery obtained through tort litigation is a necessary additional source of that information.

When the mandated studies do take place, they often result in labeling changes. In FY2014, the FDA required 61 safety actions, including 59 label changes, in light of information developed in a required postmarketing review out of the 108 reviews completed that year. Office of the Inspector General, Department of Health and Human Services, No. 01-14-00390, FDA Is Issuing More Postmarketing Requirements, But Challenges with Oversight Persist 14 (Jul. 2016). There were 32 instances of noncompliance with post-marketing requirements by manufacturers. *Id.* at 15.

FDA-ordered post-market reviews reflect a negotiated timetable with the manufacturer and can take up to seven years before the study or clinical trial is even started. *Id.* at 13. In 2015, the Government Accounting Office (GAO) found that the information the FDA does collect on post-market safety issues and studies were incomplete, outdated, inaccurate, and maintained "in a manner that made routine, systematic analysis difficult," despite an acute need for "complete, timely, and accurate information." GAO, FDA Expedites Many

Applications, at 29. The HHS Inspector General's report found that those problems persisted. *FDA Is Issuing More Postmarketing Requirements*, at 16-18.

Still, the FDA traditionally relies "on postmarket surveillance programs that passively aggregate adverse events: the FDA Adverse Event Reporting System for drugs and the Manufacturer and User Facility Device Experience Database for medical devices." Joseph Ross and Aaron S. Kesselheim, *FDA Policy and Cardiovascular Medicine*, 132 Circulation 1136, 1141 (2015), available at https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.114.010295. These databases compile adverse event reports submitted voluntarily by healthcare professionals, patients, and industry representatives to the FDA, but, as informal submissions, suffer from "incomplete, inaccurate, untimely, unverified, or biased data." *Id.* By their nature, these reports provide little basis for determining "the incidence or prevalence of an event ... because of underreporting of events and lack of information about frequency of drug or device use." *Id.* The researchers concluded that "postmarket surveillance remains a challenge with methodological and resource limitations." *Id.* at 1143.

One attempt to engage in affirmative postmarket review is the Sentinel Initiative, "which mines insurance data and medical records to identify possible risks." Sheila Kaplan, *Failure to Warn: An Early Warning System for Drug Risks Falls Flat*, STAT News (Jun. 6, 2017), https://www.statnews.com/2017/06/06/sentinel-fda-drug-risks/. However, after being in place for a

decade, "its records have been used to revise only two drugs' warning labels." *Id.* The problem that this system faces is that it seeks the information largely from insurance company billing records that rarely study people over age 65, utilize inconsistent different diagnostic codes for the same conditions, and never records deaths from medications. *Id.* The Sentinel Initiative is just another example of a program instituted to address the FDA's lack of data that has not filled the gap and highlights once again the need for the supplemental information that is the product of tort litigation.

III. NEW DRUG SAFETY INFORMATION DEVELOPS AFTER APPROVAL AND AFTER THE DRUG IS ON THE MARKET.

The heavy emphasis that Congress and the FDA has placed on speeding the premarketing approval process has caused the FDA increasingly to "approve[] new drugs and biologics on the basis of shorter, smaller, and fewer trials," Joshua D. Wallach *et al.*, *Postmarket Studies Required by the US Food and Drug Administration for New Drugs and Biologics Approved between 2009 and 2012: Cross Sectional Analysis*, 361 Brit. Med. J. k2031 (Apr. 16, 2018), available at https://www.bmj.com/content/361/bmj.k2031.
Virtually all applications are approved, and usually based on few studies of brief duration involving a modest number of subjects that are far healthier than the population targeted by the new drug. *See* David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Effort to Preempt Failure-*

to-Warn Claims, 96 Geo. L.J. 461, (2008) ("[P]re-approval testing generally is incapable of detecting adverse effects that occur infrequently, have long latency periods, or affect subpopulations not included or adequately represented in the studies (*e.g.*, the elderly, ethnic minorities and pregnant women).").

Yet, as the FDA itself acknowledges, "the true picture of a product's safety actually evolves over the months and even years that make up a product's lifetime." FDA, Step 5: FDA Post-Marketing Drug Safety Monitoring (Jan. 4, 2018), https://perma.cc/QU75-KDAC. The increased reliance on expedited pathways to FDA approval, where authorization to market the drug supported by less rigorous evidence occurs, underscores the critical role that continuous evaluation after approval plays. *See* Joshua D. Wallach *et al.*, *The US Food and Drug Administration's expedited approval programs: Evidentiary standards, regulatory trade-offs, and potential improvements*, 15 Clinical Trials 219 (Jun. 5, 2018). In a review of recent academic literature examining the expedited pathways to approval, researchers confirmed that drugs are being approved by the FDA on the basis of fewer and smaller studies, where the data contained in the NDA may lack important benchmarks that assure scientific rigor, such as use of comparator groups and random allocation, and focus on weak predictive extrapolations from the studies and trials, called surrogate markers of disease, rather than clinical outcomes. *Id.* Despite the dearth of more trustworthy testing and clinical results, the newly approved drugs "are often quickly incorporated into clinical practice, and evidence generated in the postmarket period

may not necessarily address the evidentiary limitations at the time of market entry." *Id.* Perhaps just as troubling, not all expedited pathways mandate additional postmarket studies, and drugs receiving expedited approval are associated with a greater likelihood that the FDA will need to take a safety action following entry into the market. *Id.*[11]

In fact, complete withdrawals[12] from the market because the risk-benefit analysis tilts in a different direction than the premarket data indicated are not infrequent. *See* Drug Products Withdrawn or Removed from the Market for Reasons of Safety or Effectiveness, 21 C.F.R. § §216.24, available at https://www.ecfr.gov/cgi-bin/text-idx?SID=9146635b2375a18de8912ddde721f7cb&mc=true&node=se21.4.216_124&rgn=div8.

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[11] In response to this article, the director of the FDA's Center for Drug Evaluation and Research, which is the part of the FDA that undertakes drug approvals, conceded that more is learned about a drug postmarket than at the approval stage, but emphasized the value of getting drugs to market early. Janet Woodcock, *Expediting Drug Development for Serious Illness: Trade-Offs between Patient Access and Certainty*, 15 Clinical Trials 230 (Jun. 5, 2018), available at https://journals.sagepub.com/doi/abs/10.1177/1740774518770656. A former FDA Commissioner also commented on the article, largely agreeing with the research but emphasizing that early access to new drugs and new ways of thinking about testing were needed. Robert M. Califf, *Expedited and Facilitated Drug Evaluations and Evidence of Benefit and Risk: The Cup is Half-Full*, 15 Clinical Trials 235 (Jun. 5, 2018), available at https://journals.sagepub.com/doi/abs/10.1177/1740774518771347.

[12] A withdrawal represents a decision the drug is unsafe for its intended use. 21 C.F.R. § 314.150(a)(2).

The editors of *Clinical Trials* put the problem succinctly:

> the less evidence required, the greater the risk that an ineffective or even harmful agent will be marketed, with the resulting downstream negative impact on the public health. A problematic concern is that as evidentiary standards for drug approval are lowered, the need for carefully designed and credible post-marketing studies becomes increasingly important. However, ... rigorous post-marketing research is inherently challenging and it cannot fully compensate for the kind of evidence that can only be assembled in the pre-marketing setting.

Colin B. Begg and Susan S. Ellenberg, *Expedited Approval Programs at the Food and Drug Administration*, 15 Clinical Trials 217 (Jun. 5, 2018), available at https://journals.sagepub.com/doi/full/10.1177/1740774518770653.

A recent study of pharmaceuticals and biologics approved for use by the FDA from 2001 through 2010 found that 32 percent were the subject of a "postmarket safety event," including market withdrawal or, more frequently, black box warnings and FDA safety communications to health professionals. Nicholas S. Downing, *Postmarket Safety Events among Novel Therapeutics Approved by the US Food and Drug Administration between 2001 and 2010*, 317 J. Am. Med. Ass'n 1854, 1862 (May 9,

2017), available at https://J. Am. Med. Ass'n network.com/journals/JAMA/fullarticle/2625319. The study noted that safety events were more frequent at a statistically significant rate among those drugs and biologics that had received accelerated review or were approved near the regulatory approval deadline. *Id. Cf.* Frank, 33 Health Aff. at 1458. (finding that new drugs have a "one-in-three chance of acquiring a new black-box warning or being withdrawn for safety reasons within twenty-five years of approval"). Sometimes a black-box warning is rapidly followed by the drug's withdrawal, such as when Efalizumab, a drug used to treat psoriasis, was withdrawn in 2009, a month after the black-box warning was added, because of the risk of progressive multifocal leukoencephalopathy, the same risk highlighted in the boxed warning. Downing, 317 J. Am. Med. Ass'n at 1858.

FDA scientists have conducted their own studies of the impact of the premarket approval pathways. In one, they similarly concluded that drugs approved through priority review had a higher risk of safety withdrawals or black-box warnings. *Andreas Schick et al., Evaluation of Pre-marketing Factors to Predict Post-marketing Boxed Warnings and Safety Withdrawals*, 40 Drug Safety 497 (Mar. 24, 2017), available at https://link.springer.com/article/10.1007%2Fs40264-017-0526-1. They also found that "post-marketing events are not discernible during a pre-marketing review and therefore might not be avoidable using current review data." *Id.* at 503.

Still, these studies may have substantially underestimated the frequency of these concerns because, as the Downing study points out, the researchers did not consider safety events that generated changes to labeling or to dosage. Downing, 317 J. Am. Med. Ass'n at 1862.

A group of FDA scientists examined the issue of changes to labels missing from these other studies. From a comprehensive list of postmarket safety outcomes, they found at least one safety-related update was added to 70.1% labels of the drugs studied, with the labeling change occurring as early as 160 days after approval. Ellen Pinnow *et al.*, *Postmarket Safety Outcomes for New Molecular Entity (NME) Drugs Approved by the Food and Drug Administration Between 2002 and 2014,* 104 Clinical Pharmacology & Therapeutics 390 (Dec. 20, 2017), available at https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.944. The need for a labeling change were "significantly shorter" for drugs approved through expedited pathways. *Id.* The researchers emphasized "the importance of a robust safety surveillance system throughout a drug's lifecycle and for practitioners and patients to remain updated on drug safety profiles." *Id.* at 400. Tort litigation plays a critical role, as explained *infra*, in that postmarket surveillance system.

The FDA's limitations as a monitor of pharmaceutical risk is illustrated by the frequency with which labeling changes, warning letters, and/or drug withdrawals occur. One recent study examined 222 new drugs and biologics approved by the FDA

from 2001 through 2010. Downing, *Postmarket Safety* at 1858. The study identified 123 postmarket safety events involving 71 of the new drugs and biologics. *Id.* As a result of these events, three were withdrawn from the market, 61 boxed warnings were imposed, and 59 safety communications were sent. *Id.* The median time from approval to the first safety event for that product was 4.2 years. *Id.* at 1860. Products that were withdrawn from the market stayed in circulation before withdrawal for periods of 3.4, 4.7, and 5.4 years. *Id.* The median time between approval and a boxed warning was 4.0 years, while safety communications lagged even more with a median between approval and communication of 4.9 years. *Id.*

Drugs receiving expedited review have required especially high numbers of safety-related label changes. A study published in 2017 showed that "[c]ompared with standard pathway drugs, expedited pathway drugs had a 48% higher rate of changes to boxed warnings and contraindications, the two most clinically important categories of safety warnings." Mostaghim, 358 Brit. Med. J. j3837.

IV. PHYSICIANS REQUIRE FULL AND ACCURATE INFORMATION ABOUT DRUG SAFETY TO TREAT THEIR PATIENTS SAFELY.

The Hippocratic oath mandates that physicians "prescribe regimens for the good of [their] patients according to [their] ability and judgment and never do harm to anyone" or knowingly "prescribe a deadly drug." Lisa R. Hasday, *The Hippocratic Oath as Literary Text: A Dialogue Between Law and Medicine,*

2 Yale J. Health Pol'y, L. & Ethics 299, 299-300 (2002).

To fulfill that obligation and to assure the safety of their patients, health care professionals require the best and most complete information about the drug they prescribe. The revelation of known manufacturer concerns provides critical guidance to physicians about which prescription is right for a particular patient. When the manufacturer provides the FDA with a purposely limited warning that the FDA rejects, failure-to-warn litigation can bring to light important drug safety information that has not been conveyed to medical personnel or their patients.

FDA has recognized that "it is essential to the safe use of a drug for the physician to know all adverse reactions that are likely to occur with it." Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,443 (Jun. 26, 1979). The FDA "believes that practicing physicians will welcome such information so that they can make their best informed medical judgments in the care of their patients." *Id.* at 37,447.

For that reason, the FDA requires prescription drug labeling to include a

> concise summary of the most clinically significant information ... including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug,

> and measures that can be taken to prevent or mitigate harm.

21 C.F.R. § 201.57(a)(10). The information required further includes the "most frequently occurring adverse reactions." *Id.* at § 201.57(a)(11).

In today's environment, where patients perform their own Internet research on potential drugs that may address their self-perceived problems and receive direct-to-consumer advertising from drug companies touting their latest approved drug, doctors need the most complete and well-developed information to explain benefits and risks to patients who can be insistent that their limited and often skewed information is correct and whose entreaties may be hard for physicians to resist. *See Thompson v. Western States Med. Center,* 535 U.S. 357, 383-84 (2002) (Breyer, J., dissenting). Any approach that contracts the potential sources of good information works against physicians' duties.

V. THE CIVIL JUSTICE SYSTEM SERVES AS AN IMPORTANT DOUBLE PROTECTION THAT THE FDCA ANTICIPATED WOULD SUPPLEMENT AND ENHANCE PATIENT SAFETY.

Even though drug manufacturers are obliged to report adverse events involving patients treated with a drug, *see, e.g.*, 21 C.F.R. §§ 310.305; 312.32(d)(3), 314.80, these reports may not reflect understandings of the company's doctors and scientists, who have a heightened appreciation for issues with the drug and the risks it poses. The absence of this information in the reports highlights the value that failure-to-warn

litigation serves in developing safety information known to the manufacturer but kept under wraps in reports to the FDA. Kessler and Vladeck, 96 Geo. L.J. at 491-95 (2008) (and authorities cited therein).

The existence of state tort lawsuits provides an incentive for drug manufacturers to disclose their knowledge of product risks to the FDA more fully, improving the agency's ability to assure that an adequate warning is adopted. Further, state failure-to-warn suits encourage drug manufacturers to work with the FDA to ensure that labels accurately reflect the risks associated with a given treatment. When they do not discharge that obligation, the discovery made possible through litigation can unearth internal concerns expressed by the manufacturers doctors and scientists that have not been disclosed to the FDA. *See* Aaron S. Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 297 J. Am. Med. Ass'n 308 (2007), available at https://jamanetwork.com/journals/jama/article-abstract/205083. *See also* Alex Berenson, *For Merck, the Vioxx Paper Trail Won't Go Away*, N.Y. Times, Aug. 21, 2005, at 3, available at https://www.nytimes.com/2005/08/21/business/for-merck-vioxx-paper-trail-wont-go-away.html (reporting that documents placed in evidence proved that Merck's scientists were concerned about Vioxx's cardiovascular risks as early as 1997, two years before the drug went on sale); Teresa Curtin and Ellen Relkin, *Preamble Preemption and the Challenged Role of Failure to Warn and Defective Design Pharmaceutical Cases in Revealing Scientific Fraud, Marketing Mischief, and Conflicts of Interest*, 35 Hofstra L. Rev. 1773, 1791 (2007) ("after each

development which suggested that Vioxx might pose a heightened risk of heart attacks and strokes, Merck sent special bulletins or special messages to its sales force, "directing them to use highly questionable information to assuage any physician concerns.") (citation omitted).

Traditionally, many manufacturers have downplayed known emerging safety concerns. *Id.* ("Merck sales representatives [were] trained to view doctors' concerns about Vioxx's heart risks as 'obstacles' to be avoided or dismissed.").[13] *See also* Bruce M. Psaty and Richard A. Kronmal, *Reporting Mortality Findings in Trials of Rofecoxib for Alzheimer Disease or Cognitive Impairment*, 299 J. Am. Med. Ass'n 1813, 1814-15 (2008); Bruce M. Psaty *et al.*, *Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cerivastatin and Risk of Rhabdomyolysis*, 292 J. Am. Med. Ass'n 2622, 2626-30 (2004). Civil tort trials can help reveal the unexpected effects of drugs after approval by the FDA by providing individuals with local recourse. As the FDA has limited information and capability to evaluate all possible risks of drugs after approval, state tort lawsuits play an extremely important role in ensuring that drugs on the market are safe and properly labeled. Litigation brought by individual patients can help uncover previously unavailable data on adverse effects, questionable practices by manufacturers, and flaws in regulatory

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[13] For a detailed discussion of facts learned from discovery in the Vioxx litigation and Merck's disregard for the FDA's safety concerns, *see McDarby v. Merck & Co.*, 401 N.J. Super. 10, 949 A.2d 223 (App. Div. 2008).

systems. Kesselheim and Avorn, 297 J. Am. Med. Ass'n at 308.

Product liability lawsuits and the FDA have peacefully coexisted for eighty years for one simple reason: they have complementary, rather than conflicting, goals. The tort system complements the federal regulatory structure by providing a mechanism for compensating victims of hazardous drugs. It also provides the FDA with key information unearthed in litigation that the agency can use to better protect the public from unsafe and inadequately labeled drugs. At the same time, the tort system and the FDA are similarly constrained. Whereas the FDA, as a regulatory body, weighs the risks against the benefits of a drug, in "failure-to-warn" litigation most state courts require a similar balancing between the cost of care owed to a patient versus the prospective harm. As former FDA chief counsel Margaret Porter wrote, "FDA product approval and state tort liability usually operate independently, each providing a significant, yet distinct, layer of consumer protection." Margaret Porter, *The Lohr Decision: FDA Perspective and Position*, 52 Food & Drug L.J. 7, 9 (1997).

Through discovery, litigation has regularly uncovered information about drug toxicity that would otherwise not have been known. Moreover, by levying damages for certain kinds of harm, tort law can provide powerful disincentives to risky behaviors, as well as aid the FDA in its mission. In these days of diminishing incentives to perform robust clinical trials as explained above, the products liability

system becomes a vital element in promoting compliance with the FDA's safety goals.

Even the threat of civil liability is a vital bargaining tool for the FDA in pressuring companies to amend labels to warn of newly understood risks. If pharmaceutical companies were granted almost complete immunity through federal preemption, they would have minimal incentive to report or warn of the adverse health effects of their drugs, constantly finding excuses to delay reporting or completion of required postmarketing reviews. *See* Kevin Fain *et al.*, *The Food and Drug Administration Amendments Act and Postmarketing Commitments,* 310 J. Am. Med. Ass'n 202 (Jul. 10, 2013) (finding more than 40% of studies that were supposed to be proceeding had not yet been started in 2011, the number of studies with delays doubled to approximately 1 in 8, and the proportion of all studies that have been fulfilled remains low).

In fact, given that pharmaceutical companies have been known to equate increased warnings with a loss of sales, they would have an incentive to delay warnings as long as possible. It is chilling to imagine how such companies might conduct themselves if the threat of tort liability for dangerous drugs were eliminated entirely by virtue of federal preemption.

Finally, the civil justice system has the ability to improve the lives of injured patients and their families in ways that the FDA cannot. It can provide protection in cases where the FDA is late in acting. Meritorious lawsuits can transfer the obligation to pay for the losses caused by tragic adverse events from the healthcare system to those best equipped to

pay for the injury. As bluntly stated by FDA counsel Porter, the tort system remedies the "harsh implications" of the FDA's inability to provide "recourse for consumers injured by defective" drugs. Porter, 52 Food & Drug L.J. at 9.

Rofecoxib, better known as Vioxx, is an example of litigation that brought to light previously buried data. Its manufacturer, Merck & Co., Petitioners here, claimed it was a safer than traditional nonsteroidal anti-inflammatory drugs (NSAIDs), promoting it to the point that it generated $2 billion in sales annually shortly after its introduction. Joseph S. Ross *et al.*, *Pooled Analysis of Rofecoxib Placebo-Controlled Clinical Trial Data: Lessons for Postmarket Pharmaceutical Safety Surveillance*, 169 Archives Internal Med. 1976, at *1 (2009), available at https://pdfs.semanticscholar.org/2784/8d1bb790a603cf9b2ca5740cc4f1c9bcf2e8.pdf. However, five years after its introduction, Merck voluntarily withdrew the drug from the market after studies showed significant cardiovascular risk. *Id.* Still, what hastened its withdrawal was the revelation in discovery that Merck's own researchers had expressed that precise concern before Vioxx hit the market. *Id.*, citing E.M. Scolnick, E-mail communication to Deborah Shapiro, Alise Reicin, and Alan Nies re: vigor [Bates No. MRK-ABH0016219, *Cona v. Merck & Co Inc*], Mar. 9 2000, http://dida.library.ucsf.edu/pdf/oxx00c10.

Other high-profile cases include:

- Baycol (cerivastatin): "manufacturer allegedly suppressed knowledge that patients were

developing a potentially life-threatening muscle disease, and that the risk of such condition increased with higher dosages at the time the company was negotiating with the FDA for approval of the drug at higher dosages." Curtin and Relkin, 35 Hofstra L. Rev. at 1783 & n. 55 (and accompanying text);

- Bextra (valdecoxib): Pfizer engaged in deceptive marketing by failing to warn increased cardiovascular risks and potentially life-threatening skin reactions, while falsely claiming Bextra provided superior pain relief and safety than traditional NSAIDs. *In re Bextra and Celebrex Mktg. Sales Practices and Prod. Liab. Litig.*, No. CV-05-1699, 2006 WL 2472484, at *2 (N.D. Cal. Aug. 24, 2006);

- Ortho Evra: manufacturer accused of misrepresenting that birth control contraceptive patch was as safe as oral contraceptives even though it knew or should have known that it could cause blood clots. Martha Mendoza, "Warning Issued for Birth-Control Patch," Wash. Post, November 11, 2005, available at http://www.washingtonpost.com/wp-dyn/content/article/2005/11/11/AR2005111100242.html (discussing documents made available through litigation);

- Paxil (paroxetine): manufacturer allegedly suppressed studies indicating increased suicidal behavior, while releasing the favorable study. Press Release, Office of the New York State Attorney General, Major Pharmaceutical

Firm Concealed Drug Information: GlaxoSmithKline Misled Doctors About the Safety of Drug Used to Treat Depression in Children (Jun. 2, 2004), available at http://www.oag.state.ny.us/press/2004/jun/jun2b_04.html; *see also* Jon N. Jureidini *et al.*, *Clinical Trials and Drug Promotion: Selective Reporting of Study 329*, 20 Int'l J. of Risk & Safety in Medicine 73 (2008) (detailing how documents obtained in litigation contradicted GlaxoSmithKline's claim that Study 329 showed that "paroxetine is generally well tolerated and effective for major depression in adolescents.") [14].

- Zyprexa (olanzapine): manufacturer hid adverse side effects from use of anti-psychotic drug. *In re Zyprexa Prod. Liab. Litig.*, 489 F. Supp. 2d 230 (E.D.N.Y. 2007).

It is indisputable that the civil justice system plays a critical role in exposing otherwise unknown or unrevealed adverse effects in approved drugs.

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[14] Paxil is the drug at issue in *Dolin v. GlaxoSmithKline LLC*, 901 F. 3d 803 (7th Cir. 2018), which both parties discuss. In considering what the Seventh Circuit did in that case, it is important to remember that appropriate warnings that apply across the board to a class of pharmaceuticals still may not be sufficient when discussing a particular drug within that class. *See Dolin v. GlaxoSmithKline, LLC*, 269 F. Supp.3d 851, 864 (N.D. Ill. 2017); *Forst v. Smithkline Beecham Corp.*, 639 F. Supp. 2d 948, 954 (E.D. Wis. 2009) ("In denying the proposed language, the agency did not prohibit all enhanced warnings. Instead, the FDA merely required removal of Paxil-specific language from a particular portion of Paxil's label in favor of uniform class-wide labeling for all SSRI's.")

Through discovery, litigation has regularly uncovered information about drug toxicity that would otherwise not have been known outside the companies that manufactured the drug.

By levying damages for certain kinds of harm, tort law can provide powerful disincentives to risky behaviors, as well as aid the FDA in its mission. Even the threat of civil liability is a vital bargaining tool for the FDA in pressuring companies to amend labels to warn of newly understood risks. If pharmaceutical companies were granted almost complete immunity by virtue of federal preemption, they would have minimal incentive to report or warn of the adverse health effects of their drugs – or to propose warnings as appropriate as the research suggests. In fact, given that pharmaceutical companies have been known to equate increased warnings with a loss of sales, they would have an incentive to delay warnings as long as possible or to claim that the proposal of inadequate warning should foreclose a more adequate one.

Finally, it should not go unremarked that the civil justice system has the ability to improve the lives of injured patients and their families in ways that the FDA cannot. It can provide protection in cases where the FDA is late in acting. It can provide critically important compensation to those whose lives are devastated by undisclosed drug risks.

The academic research demonstrates the need to permit tort litigation to fill gaps and expose hidden

information about prescription drugs on the market. Limiting the reach of *Wyeth* would operate against that important public health imperative. Enforcing it, however, assures that a manufacturer does not have an incentive to withhold information or submit a patently inadequate warning with the expectation that rejection will earn a free pass against tort liability. It should not be enough to hint at a more appropriate warning secure in the knowledge that the FDA will usually neither approve the insufficient one nor develop its own. No safe harbor from liability should be recognized if the proposed, but rejected warning fails to alert physicians and patients of real and known dangers. The bottom line is that tort litigation plays a crucial role in the postmarket surveillance of drug risks and one that should not be curtailed by impact of the lessons of *Wyeth*.

CONCLUSION

For the foregoing reasons, amici curiae respectfully request that the decision of the Third Circuit be affirmed.

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No. 17-290

IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

DORIS ALBRECHT, ET AL.,
Respondents.

On Writ of Certiorari to
the United States Court of Appeals
for the Third Circuit

BRIEF OF *AMICI CURIAE* JOSEPH LANE, M.D., AND VINCENT VIGORITA, M.D., IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICI CURIAE* AND SUMMARY OF ARGUMENT[1]

An improper understanding of osteology frames Petitioner's bid for legal immunity. Petitioner claims that the language it proposed to warn of stress fractures would also have warned of atypical femur fractures associated with long-term use of the osteoporosis drug Fosamax (a bisphosphonate). Petitioner thus argues that it is clear FDA would have rejected a label change that would have warned of atypical femur fractures because FDA declined to approve a proposed label change concerning stress factures.

That legal argument misconceives medical science. Stress fractures are radiographically and symptomatically different from atypical femur fractures associated with long-term use of Fosamax. The particular language Petitioner proposed in a Prior Approval Supplement (PAS) to warn of "stress fractures"—an incomplete fracture that generally presents in non-bisphosphonate patients and typically heals on its own—cannot reasonably be read to warn of atypical femur fractures—a complete break in the bone that is associated with long-term use of Fosamax, and that requires surgery.

Amici curiae are physicians with expertise in metabolic bone disorders, other bone diseases, and the pathology of bone diseases. *Amici* have a strong interest in this case because legal immunity from failure-to-

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[1] No counsel for a party authored this brief in whole or in part and no person other than *amicus* and its counsel made a monetary contribution to its preparation or submission. The parties' letters consenting to the filing of *amicus* briefs are on file with the Clerk.

warn liability may turn on a proper understanding of osteology.

Joseph Lane, M.D., received his undergraduate degree from Columbia College, his medical degree from Harvard Medical School, and undertook his surgical internship and residency at the Hospital of the University of Pennsylvania. Dr. Lane performed bone collagen research at the National Institutes of Health (NIH) from 1967 to 1969. In 1975, Dr. Lane was appointed Assistant Professor and Chief of the Metabolic Bone Disease Service at the Hospital for Special Surgery of Cornell Medical School (HSS). HSS is nationally ranked as the number one center for orthopedics by U.S News & World Report.[2] Dr. Lane ultimately attained a full professorship and currently serves as the Medical Director of the Metabolic Bone Disease Service and Osteoporosis Prevention at HSS. Dr. Lane has authored or co-authored over three hundred peer-reviewed articles in areas such as bone biology, tissue injury and repair, trauma, and metabolic bone disease.

Dr. Lane has served on numerous committees for the American Academy of Orthopaedic Surgeons (AAOS), including its Board of Directors and as Chairman of the Council on Musculoskeletal Specialty Societies. Dr. Lane previously served as the President of the Orthopaedic Research Society and as the Chairman of the NIH Orthopaedic Study Section. In 2008, Dr. Lane co-authored the retrospective study from

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[2] https://www.usnews.com/info/blogs/press-room/articles/2018-08-14/us-news-announces-2018-19-best-hospitals

HSS which found that long-term alendronate[3] use resulted in an atypical femur fracture odds ratio of 139.33; more simply, patients taking long-term alendronate had an odds ratio for this unusual fracture pattern which was 139 times higher (13,900%) than those studied patients not taking alendronate. Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use.* 22 J ORTHOP. TRAUMA 346-50 (May-June 2008).[4] In addition to presenting the study's preliminary findings, Dr. Lane and his co-authors published their research in the New England Journal of Medicine in March 2008. Lenart, *Atypical Fractures of the Femoral Diaphysis in Post-Menopausal Women Taking Alendronate*, 358 NEJM 1304-06 (March 2008).[5]

In 2005, three years before that publication, Dr. Lane reported to Petitioner that no fewer than twenty-five HSS patients had suffered from low-energy *atypical* femur fractures. Dr. Lane also told Petitioner that physicians at this hospital call this type of fracture the "Fosamax fracture."[6] In 2008, Dr. Lane served as a consultant to Petitioner during the time when Petitioner was determining how it would prepare the requested drug label change pertaining to reports of fractures in patients taking Petitioner's medication,

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[3] Petitioner's Fosamax is the trade name for the drug alendronate.

[4] JA385-399.

[5] JA661-663.

[6] JA445-449, at 448.

Fosamax.[7] Dr. Lane's reports to Petitioner contributed to the need for Petitioner to provide a warning or precaution to prescribers of Fosamax.

In the spring of 2009, the American Society for Bone and Mineral Research (ASBMR) commissioned a Task Force on Subtrochanteric Fractures. JA97-98 (Burr Decl.¶4); JA283-384 (Shane, *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society of Bone and Mineral Research*, 25 J BONE MINER RES. 2267-2294 (2010)). Dr. Lane served as a member of the task force. JA283. Its first report was published in September 2010.[8] JA285.

In 2011, HSS presented Dr. Lane with its Lifetime Achievement Award for his innovative research on bone disease and the use of bisphosphonates in treating osteoporosis and, more specifically, his research which helped identify the association between long-term use of bisphosphonates and the increased risk for certain bone fractures.[9]

Vincent Vigorita, M.D., received his undergraduate degree from Williams College and his Medical Degree from New York Medical College. He performed his internship and residency at The Johns Hopkins Hospital, and his fellowship at the Memorial Sloan Kettering Cancer Center. Dr. Vigorita is Professor Pathology

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[7] JA467-468.

[8] A follow-up report was published in 2014. Dr. Lane was also a co-author of this second report. Shane, *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society of Bone and Mineral Research*. 29 J BONE MINER RES. 1-23 (2014).

[9] https://www.hss.edu/newsroom_joseph-m-lane-lifetime-achievement-award.asp

& Orthopedic Surgery at the State University of New York Health Science Center, Downstate, in Brooklyn, New York. Since 1980, Dr. Vigorita has been a Diplomat of the American Board of Pathology. From 1983 to 1992, Dr. Vigorita was visiting scientist in the division of research at HSS. He has authored or co-authored more than eighty peer-reviewed medical articles pertaining to various aspects of bone disorders and pathology, including articles he co-authored with Dr. Lane on metabolic bone disease (osteoporosis). Dr. Vigorita is the author of the medical textbook *Orthopaedic Pathology*, which is in its Third Edition. In 2010, he was invited to present to the International Skeletal Society on the topic of dysfunctional osteoclast activity and bisphosphonate treatment. In 2012, Dr. Vigorita was the lead author of a peer-reviewed case report pertaining to pathologic features of fractured bone during bisphosphonate therapy. Vigorita, *Osteoclast Abnormalities in Fractured Bone During Bisphosphonate Treatment for Osteoporosis: a Case Report*, 41 SKELETAL RADIOL. 861-65 (2012).

ARGUMENT

I. Petitioner's Proposed Warning of Stress Fractures Did Not Warn of Atypical Femur Fractures.

Dr. Lane's reports to Petitioner, as well as his and others' publications in peer-reviewed medical literature, contributed to the need for Petitioner to provide a precaution to prescribers of Fosamax about atypical femur fractures. In 2005, Dr. Lane told Petitioner that no fewer than twenty-five HSS patients had suffered from low-energy *atypical* femur fractures. Later, in the summer of 2008, Dr. Lane served as a consultant to Petitioner when it was considering adding a warning to address reports of these unusual fractures. JA464-476. Petitioner's own meeting minutes leave little doubt that the fractures reported by Dr. Lane's group were atypical femur fractures, not mere stress fractures. *See* JA468.

In September 2008, Petitioner submitted a PAS proposing to add language to the *Warnings and Precautions* section of Fosamax's label. The proposal emphasized "stress fracture(s)" six times, including in a statement that "stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonate." JA707.

On May 22, 2009, FDA informed Petitioner in writing that it had rejected Petitioner's proposal. JA510-514. Specifically, FDA told Petitioner that "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." JA511.

Petitioner's focus on "stress fractures" in proposed labeling would not have conveyed to physicians and patients what Dr. Lane had reported to Petitioner: Fosamax patients were experiencing serious fractures that orthopedic physicians had not previously seen.

A. The femur and fractures: a medical overview.

1. The femur is the thigh bone in the human body. If you have seen a "skull and cross-bones," such as on pirate flag, you have seen a depiction of two thigh bones.

The end of the femur closest to the torso is called "proximal"; and the opposite end most distant from the torso is called "distal." The portion closest to the torso resembles a ball on a neck; we call this the "femoral head." The femoral head joins the pelvis at the socket, or "acetabulum." Together, the femoral head and acetabulum comprise the hip joint.

The portion of the proximal femur which resembles a neck for the head is called the "femoral neck." The neck connects the femoral head to what appears as a hump on the top of the long shaft of the femur. This hump is called the "greater trochanter" on the top end, and the "lesser trochanter" on the bottom end of the hump where it connects to the straight portion of the bone. The term "subtrochanteric" refers to the portions below, which together form the "trochanter."

Viewing the femur a step removed, you see that the head connects to the neck, which connects to the trochanter, which connects to a straight, long shaft of bone. That portion of the bone is called the "diaphysis." It connects to the bulb-looking distal end of the femur through the end of the shaft (the "metaphysis"),

and flares out and connects to the bulbous portions of the end of the bone, the "lateral and medial epicondyles," terminating at the "lateral and medial condyle."

Like most bones, the femur is comprised of the "cortex," or "cortical bone," which is the outer, hard-candy shell of the bone surrounding another type of bone called the "cancellous" or "trabecular" bone. Cancellous bone is a spongy type of bone situated in the interior of the bone; it is the portion of our bones responsible for producing bone marrow. The portion of the bone where the cancellous bone is found is often referred to as the "medullary canal," and surgical approaches which ream out that canal and place hardware are referred to as "intramedullary reaming."

2. Fractures follow different patterns. A "transverse" fracture refers to a fracture that goes across the shaft of the bone; in other words, from one side of the cortical bone, across the medullary canal containing the cancellous bone, and then to the other side of the cortical bone. An "oblique" fracture proceeds across the bone in an angled fashion. A "stress fracture" refers to a hairline crack in which portions of the bone on either side of the crack are not displaced from each other. A "displaced" or "completed" fracture refers to a fracture where two or more fragments of bone are no longer joined to the other fragment.

"Stress fractures" can progress to a displaced or completed fracture. A "traumatic fracture" is one which results from trauma or an exertion of significant force on the bone, and it typically results in a completed or displaced fracture. A "low-energy" fracture,

in contrast, is a fracture that occurs without significant trauma.

B. Petitioner's proposed warning about stress fractures did not accurately convey what it knew about atypical femur fractures.

The FDA was concerned about Petitioner's repeated focus on the term "stress fracture," and rightfully so. The medical literature addressed *atypical* femur fractures that may have started as a simple stress fracture but progressed to something far more serious than a garden-variety stress fracture. But Petitioner chose to craft a warning emphasizing stress fractures and risks associated with stress fractures, even though that language did not reflect the unusual clinical outcomes Fosamax patients were experiencing.

"'Stress fractures,' in the medical community, commonly refers to an *incomplete* fracture of a long bone which is clinically diagnosed by pain in the affected region, an x-ray or MRI showing a periosteal or endosteal reaction, and/or a bone scan showing increased local metabolic activity in the painful region. JA144 (Burr Decl. ¶83) (emphasis added).[10] Because "the vast majority of stress fractures never progress to a full and complete fracture," *id.*, a stress fracture is distinguishable from an atypical femur fracture, which results in a *completed* femoral fracture. *See* JA101-02 (Burr Decl. ¶12).[11]

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[10] Dr. David Burr was the Co-Chair of the ASBMR Task Force and served as to the co-editor of the medical textbook entitled Musculoskeletal Fatigue and Stress Fractures (2001). JA144.

[11] The only mention of "stress fracture" in either of Dr. Lane's publications predating Petitioner's PAS noted an atypical femur fracture that was "propagated" from a stress fracture which had

X-rays of stress fractures and atypical femur fractures illustrate these differences. Look first at an image of a stress fracture in a femur:[12]

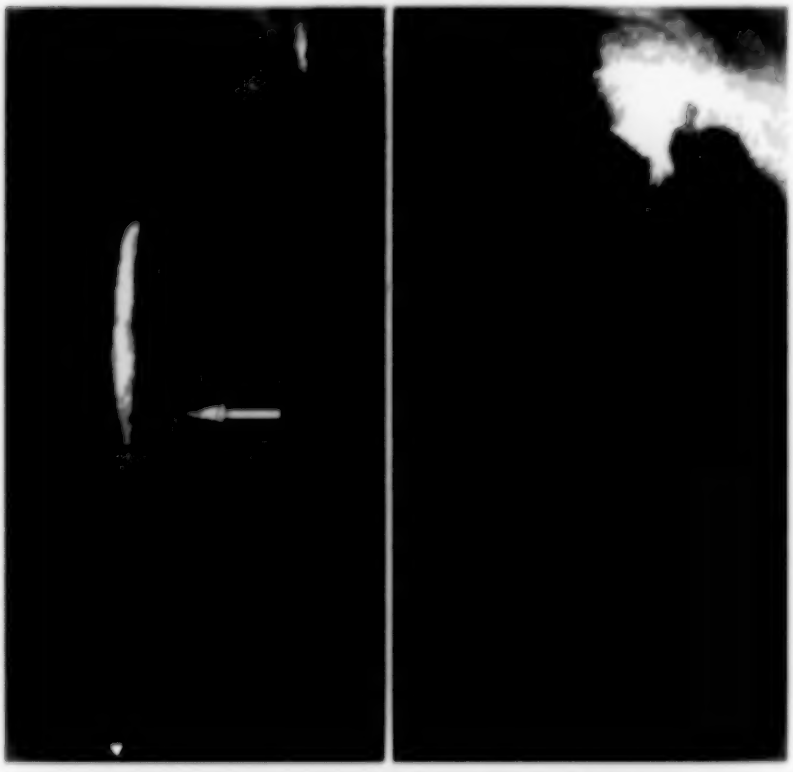

Figure 1 Anteroposterior and lateral roentgenograms showing stress fractures in the proximal third of the right femoral shaft (white arrow).

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failed to heal due to Fosamax. (JA385, 396 (Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use*).

[12] Ivkovic, *Stress Fractures of the Femoral Shaft in Athletes: a New Treatment Algorithm*, 40 BR J SPORTS MED 518-520 (2006), at fig. 1.

Look next at radiographs of atypical femur fractures in three patients:[13]

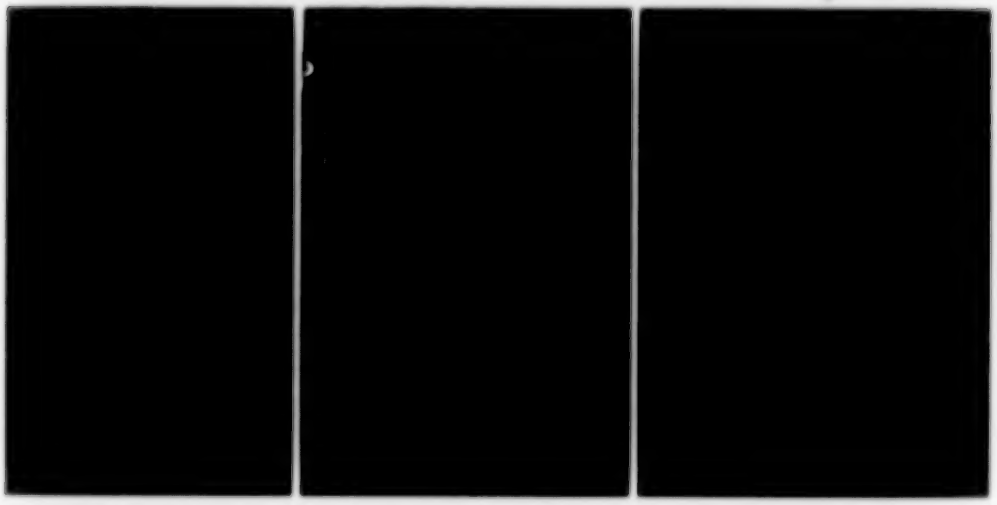

FIGURE 1. Representative radiographs of femoral shaft fractures sustained from minimal trauma in patients taking alendronate. Although each radiograph demonstrates the pattern in its entirety, we have highlighted the following features. A, Fracture pattern pictured with an arch measuring 30 degrees to highlight transverse nature. B, The arrow pointing out the unicortical beak C, Hypertrophied cortices outlined.

In this second set of images, a fracture pattern runs across the bone, and—atypically—involves a thickening (hypertrophy) rather than a thinning of the cortical bone by the fracture sites. JA661-663 (Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use*); JA385, 387-89 396 (Lenart, *Atypical*

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[13] Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use*, 22 J ORTHOP TRAUMA 346-50, at fig. 1 (May/June 2008).

Fractures of the Femoral Diaphysis in Post-Menopausal Women Taking Alendronate).

FDA was aware of the Neviaser and Lane article. In June 2008 (*see* JA666-67), FDA emailed Petitioner to say "we are aware of reports" regarding "[t]he subtrochanteric type of hip or femoral fracture" that "is reportedly rare in patients with osteoporosis not on bisphosphonates. We are concerned about this developing safety signal." That email listed five studies, with the Neviaser and Lane study listed first.

Although *amici* and colleagues "identif[ied] a fracture that is specific to patients being treated with alendronate and tends to occur after use of more than 4 years," JA393 (Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use*), Petitioner failed to present FDA with language that warned of such atypical fractures.

FDA acted appropriately when it rejected the language on stress fractures and invited Petitioner to "resubmit" its application after "fully address[ing] all the deficiencies listed." JA512. The term "stress fracture" conveys to the prescriber a fracture which typically can be treated conservatively, meaning, without surgery. Generally, doctors treat stress fractures in patients by prescribing rest or inactivity in the affected bone. Most stress fractures heal without any further intervention and do not progress to a complete fracture. JA144 (Burr Decl. ¶83).

But that is not what the medical community observed in certain Fosamax patients. An atypical femur fracture may start as a stress fracture, but it will not heal on its own (as a stress fracture might). And it progresses to a fully displaced fracture of the femur

(unlike a stress fracture which typically is incomplete).[14]

Once these complete fractures occur, the clinical outcome far exceeds what a patient with just a stress fracture experiences. "Because of the propensity for delayed healing, the morbidity [or medical problems] of these [atypical subtrochanteric and femoral shaft] fractures is particularly high." JA349.

Complete fractures require invasive surgery. An open reduction, internal fixation surgery of an atypical femur fracture involves the physician cutting through the patient's skin, fat, and muscle, and reaming out much of the cancellous bone in the medullary canal. A long rod is then hammered into place in order to reduce the fracture (or bring the bone fragments back into relative alignment). The rod is secured with bone screws. JA350.

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[14] "Low-energy fractures of the femoral shaft with a simple, transverse pattern and hypertrophy of the diaphyseal cortex are associated with alendronate use. This may result from propagation of a stress fracture whose repair is retarded by diminished osteoclast activity and impaired microdamage repair resulting from its prolonged use." JA386 (Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use*).

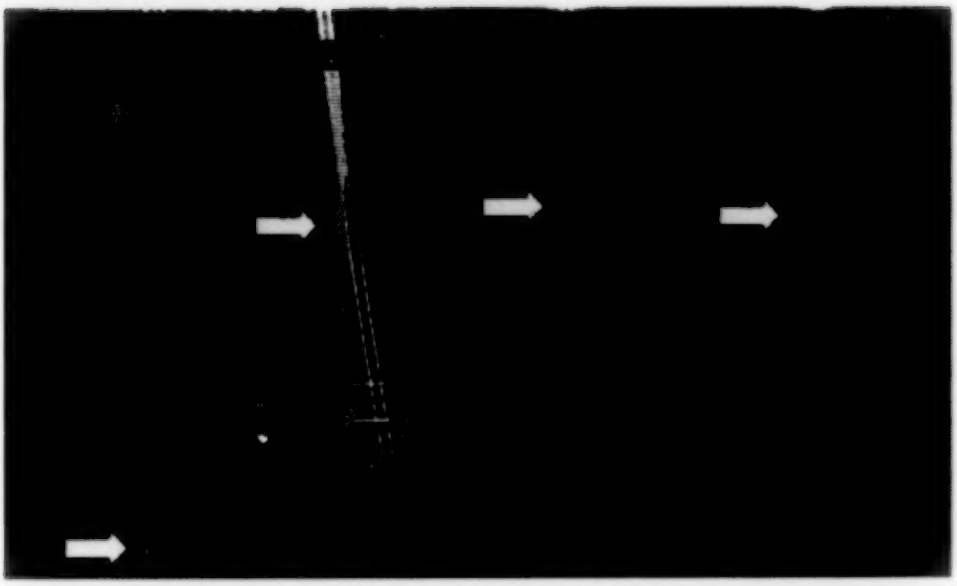

FIGURE 1. Representative radiographs of femoral shaft fractures sustained from minimal trauma in patients taking alendronate. Although each radiograph demonstrates the pattern in its entirety, we have highlighted the following features. A, Fracture pattern pictured with an arch measuring 30 degrees to highlight transverse nature. B, The arrow pointing out the unicortical beak C, Hypertrophied cortices outlined.

The patient typically has this hardware in place for the rest of her life.[15]

This type of clinical result in a patient who has undergone no or minimal initiating trauma is in part what makes these fractures atypical. JA661. *Amici* thus wholeheartedly agree with Dr. Burr: "By choosing to characterize [atypical femur fractures] as 'stress

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[15] Shane, *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society of Bone and Mineral Research*. 29 J BONE MINER RES. 1-23, at fig. 1 (2014).

fractures' in its submission to the FDA, Merck improperly conflated the underlying fracture mechanism that leads to [atypical femur fractures] with the ultimate outcome." JA144 (Burr Decl. ¶84).

C. Petitioner's proposed warning failed to identify the association between Fosamax and atypical femoral fractures.

These femoral fractures are also atypical in the sense that orthopedic physicians had not seen these fractures before Fosamax or other bisphosphonate drugs were marketed. JA101-02 (Burr Decl. ¶12).

The incidence of such unique fractures came to the medical community's attention "principally in the setting of [bisphosphonate] use"; by comparison, the "incidence in the general population not exposed to [bisphosphonates] is unknown." JA291 (ASBMR Task Force Report). Atypical femur fractures are observed in Fosamax patients because Fosamax, by design, interferes with the removal of old bone and the replacement of that bone with new bone. The goal of this drug regimen is to preserve bone mineral density. But when the drug is administered to patients for lengthy periods, the bone can become more dense and, at the same time, less resilient to fracture. JA103-109 (Burr Decl., ¶¶15-23). By interfering with the bone turnover process, bisphosphonates can interfere with the healing of non-displaced stress fractures. JA136 (Burr Decl. ¶ 68) ("Fosamax and other BPs reduce the body's ability to repair a stress fracture once it has begun, but prior to complete fracture.").

As early as 2002, Dr. Lane and his colleagues began describing these atypical femoral breaks as "Fosamax fractures;" and they informed Petitioner of this in 2005.

In 2005 and 2007, two published case series "suggested a link between prolonged bisphosphonate therapy and atypical fractures." JA661.[16] And, beginning in 2005, Dr. Lane and his colleagues shared, with Petitioner, their preliminary findings on atypical fractures in Fosamax patients. Their research was ultimately published in 2008 in the New England Journal of Medicine.

"[A]lthough different studies and authors have used slightly different variations on how they describe [atypical femur fractures]," Dr. Burr has concluded (and we agree), "there is, and was before September of 2008, remarkable consistency in the overall description of this unique fracture and its high association in the literature with Fosamax and other bisphosphonates. JA139-140 (Burr Decl. ¶74).

Despite this, Petitioner proposed a warning that these fractures had "similar clinical features" to fractures suffered by non-bisphosphonate patients. *See* JA138. This proposal failed to convey the unique features of these fractures. FDA was thus right to reject Petitioner's proposed warning.

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[16] Goh, *Subtrochanteric Insufficiency Fractures in Patients on Alendronate Therapy: A Caution*, 89-B J BONE AND JOINT SURG 349-53 (2007) (JA400-14); Odvina, *Severely Suppressed Bone Turnover: A Potential Complication of Alendronate Therapy*, 90 J CLIN ENDOCRINOL METAB 1294-1301 (2005) (JA415-444).

D. There is compelling evidence that FDA would have approved a label change that warned of atypical femur fractures associated with Fosamax.

1. Petitioner's description of stress fractures in its July 2008 labeling submission was medically inconsistent with the atypical femur fractures that *amici* and other physicians around the world had observed. In fact, FDA recognized this distinction in rejecting Petitioner's proposal.

FDA indicated that it was aware of the potential for Fosamax to cause atypical femur fractures. On June 13, 2008, an FDA staff member notified Petitioner that FDA was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates." JA666. FDA was referring to five published articles in the medical literature; Dr. Lane's was the first listed. JA667. None of these articles focused on ordinary stress fractures; rather, all described atypical femur fractures associated with Fosamax.

Also on June 13, FDA asked Petitioner to submit "all hip and femoral fracture" reports it had received to date. JA666. Notably, FDA did not seek any information focused specifically on the atypical features seen prominently in patients in the published medical literature. FDA's request did not draw attention to the unique transverse fracture pattern, the absence of trauma associated with the fractures, or the suppressed bone remodeling seen in many atypical femur fracture patients. These omissions suggest FDA did not yet fully understand the nature of atypical femur fractures and was in need of a medically accurate education on the subject.

In late June 2008, Petitioner asked Dr. Lane and other medical experts to discuss the state of knowledge on atypical femur fractures. By that time, Petitioner had amassed a growing number of atypical femur fracture adverse event reports. Indeed, as early as 2005, Dr. Lane had reported "25 patients with long bone fractures that have taken Fosamax ... for a long time. He also reported that 100% of patients in his practice who have experienced femoral fractures (without being hit by a taxicab) were taking Fosamax ... for over 5 years. At [his] hospital they call it the 'Fosamax Fracture.'" JA126. This June 2008 meeting was held soon after Dr. Lane and his colleagues publicized that long-term Fosamax use resulted in an odds ratio of 139.33 for suffering an atypical femur fracture when compared to patients that had never taken Fosamax. JA385-386 (Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use.* 22 J ORTHOP TRAUMA 346-50 (May/June 2008)).

Petitioner's medical consultants confirmed that the fractures Dr. Lane and others had observed should not have been be characterized as stress fractures, and that instead the observed fractures presented more consistently as insufficiency fractures. JA467-468. The consultants also explained the distinction between, on the one hand, the insufficiency fractures seen in Fosamax patients; and on the other, stress fractures. The consultants advised Petitioner that "insufficiency fractures occur *with normal activity in abnormal bone.*" JA467 (emphasis in original). Conversely, "stress fractures may be caused by *increased activity in normal quality bone.*" JA467 (emphasis in original). Nevertheless, Petitioner's proposal focused on stress fractures, with the phrase repeated six times. JA707.

2. Petitioner's proposed warning language improperly focused solely on the originating element of the fracture (the stress injury), rather than ultimate outcome (the atypical femur fracture). As such, the proposed language elided critical distinctions between incomplete and complete factures, and the corresponding injury and medical treatment.

Another problem with Petitioner's proposal: It omitted any discussion of the pathogenesis of atypical femur fractures. Language advising of the severity of the break would have distinguished a Fosamax associated fracture from typical osteoporotic fracture.

By September 2008, there was a robust body of medical literature demonstrating that Fosamax significantly suppresses bone remodeling, which severely decreases bone toughness and reduces the body's ability to recover from a stress injury. Rather than provide this information about the pathogenesis of this atypical fracture, Petitioner cautioned the reader of its proposed warning to conduct an "evaluation for known causes and risk factors (*e.g.*, vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse)." JA707. But these risk factors are associated with stress fractures—not atypical femur fractures. *See* JA142 (Burr Decl. ¶ 79)

Further, Petitioner's language failed to document the association of atypical femur fractures with long-term Fosamax use. Reports of atypical femur fractures both before and after September 2008 have generally been seen in patients using the drug for five years or more. This information would have distinguished an atypical femur fracture from a minor stress

fracture, and would have prompted due consideration of the risks and benefits of long-term use of Fosamax.

Still more, Petitioner's proposed language improperly suggested there was an established background rate for atypical femur fractures in patients not exposed to Fosamax. This suggestion was not supported by medical evidence, and it erroneously conflated typical fractures seen in the osteoporotic population with so-called Fosamax fractures.

Lastly, Petitioner made no effort in its proposed language to define atypical features of these fractures. By September 2008, many publications had adequately described atypical femur fractures as being low energy fractures occurring along the femoral shaft or subtrochanteric regions of the femur, with a transverse fracture line, a periosteal reaction, associated with cortical thickening, prodromal pain, and frequently seen bilaterally. But these valuable insights were not reflected in Petitioner's proposed language.

3. There is little doubt Petitioner understood the deficiencies in its proposals. Upon receiving FDA's Complete Response letter, Petitioner's employee James Adams acknowledged that FDA "believed that our justification to support the proposed Precaution text was inadequate. *It believes that 'stress fractures' may not be clearly related to atypical subtrochanteric fractures.*" JA515 (emphasis added). Petitioner's most senior scientist responsible for Fosamax, Dr. Arthur Santora, reacted similarly: "FDA wouldn't let us mention stress fractures." JA517.

Following these exchanges, a task force consisting of 28 individuals formed by the American Society for Bone and Mineral Research met to synthesize the known evidence concerning atypical femur fractures.

JA287. FDA noted, in March 10, 2010, that it was working with this task force to "gather additional information that may provide more insight into this issue." JA519-520. The task force acted quickly to evaluate the existing evidence and ultimately created a list of major and minor features associated with atypical femur fractures. JA292. Importantly, nearly all of the evidence the task force reviewed was equally available to Petitioner when it proposed its labeling update in September 2008. In the end, the task force's report referenced 177 medical journal articles—172 more than had been previously made available to FDA. JA359-384; JA667.

On the same day that the task force published its findings, FDA publicly acknowledged that the case definition for atypical femur fractures created by the task force would "help greatly in identifying cases and reporting on them." JA523. The FDA also indicated it was "considering labeling revisions." JA525.

Less than one month later, FDA issued another public statement on atypical femur fractures. In this statement, FDA announced that information on atypical femur fractures would be added to the *Warnings and Precautions* section of labeling for bisphosphonates, including Fosamax. JA246. FDA's description of atypical femur fractures included detail lacking in Petitioner's earlier proposal.

On October 13, 2010, FDA asked Petitioner to update labeling for Fosamax to include a warning about atypical femur fractures. JA527. In response, Petitioner again proposed warning language that focused heavily on stress fractures and attendant risk factors associated with stress fractures. JA606-607.

FDA rejected aspects of Petitioner's proposal shortly thereafter, on December 16. Critically, the agency deleted *all* references to stress fractures, and *all* references to risk factors associated with stress fractures but not seen with atypical femur fractures. JA606-607. Current labeling for Fosamax makes no reference to stress fractures or risk factors associated with stress fractures.

The agency took this action because, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use. In addition, the risk factors listed in the proposed changes have not been sufficiently validated to include in labeling at this time." JA566.

This would hardly have come as a surprise to Petitioner. After all, FDA had rejected Petitioner's stress-fracture warning of 2008 because its "[i]dentification of 'stress fractures'" and "[d]iscussion of the risk factors for stress fractures" was not supported by the state of medical knowledge at that time (JA511-12)—including as reported in the Neviaser and Lane article. *See* JA666-67.

CONCLUSION

The judgment of the court of appeals should be affirmed.

Respectfully submitted,

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No. 17-290

IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,

Petitioner,

v.

DORIS ALBRECHT, *et al.*,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Third Circuit

BRIEF OF MEDSHADOW AND FORMER FDA OFFICIALS AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF AMICI CURIAE

MedShadow Foundation is an independent, not-for-profit organization whose mission is to ensure people have access to independent information on the side effects and adverse events of medicines in order to balance the benefits and the harms of medicines. MedShadow provides clear, evidence-based information to help people better understand the harms and benefits of the medicine they are taking or may be prescribed so that they can take a more active role in their healthcare. The organization's goal is to save lives by minimizing the harm caused by, and decreasing the unnecessary use of, medicines.

Joshua M. Sharfstein M.D. served as the Principal Deputy Commissioner at the Food and Drug Administration ("FDA") from March 2009 until January 2011. Mary K. Pendergast J.D., LL.M., served as Deputy Commissioner and Senior Advisor to the Commissioner at FDA from November 1990 until December 1997 and as Associate Chief Counsel for Enforcement in the Office of the General Counsel from July 1979 until November 1990. Jeremy Sharp served as the Deputy Commissioner for Policy, Planning, Legislation and Analysis from June 2015 until January 2017. Dr. Sharfstein, Ms. Pendergast, and Mr. Sharp are experts in the regulatory procedures applicable to drugs.[1]

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[1] The parties have consented to the filing of this brief. No counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amici curiae*, its members, or its counsel made a monetary contribution to its preparation or submission.

INTRODUCTION

Respondents in this case are patients who allege that petitioner's drug, Fosamax (alendronate sodium), caused them to suffer atypical femoral fractures ("AFFs"), which are incapacitating fractures that result from little or no trauma in which the thigh bone, or femur, often breaks in two. J.A. 288-89, 292. Fosamax belongs to a class of drugs called "bisphosphonates," which are commonly used to treat osteoporosis. J.A.192; Pet'r App. 5a. Respondents claim, among other things, that petitioner Merck Sharpe & Dohme Corp. ("Merck) failed to warn of AFFs, which respondents contend was required by state law. Merck argues that it sought to add such a warning, that the Food and Drug Administration ("FDA") in a final irreversible decision rejected that warning, and that, because federal law prohibited it from warning about AFFs until October 2010, respondents' claims are preempted by federal law. Pet'r Br. at 31, 34.

Merck's argument that respondents' claims are preempted turns on: whether Merck ever requested that FDA allow Merck to add a warning for AFFs; whether FDA ever rejected such a request; and whether Merck could have added the warning to its label without waiting for FDA approval or requested FDA's authorization to do so. This brief will demonstrate that a review of the FDA record shows that while Merck did seek to add a warning regarding "low energy femoral shaft fractures" and specifically "stress fractures," which are more common and less severe than AFFs, it never attempted to add a warning for AFFs, and that FDA never made a decision that would have barred Merck

from adding a warning about AFFs to its label with or without waiting for FDA approval.

BACKGROUND

FDA approved Fosamax in 1995 to treat osteoporosis and in 1997 to prevent osteoporosis. Pet'r App. 5a, 12a-13a. Between 1999 and 2002, Merck received adverse event reports indicating that long-term Fosamax users were suffering from atypical femoral fractures. J.A. 122-25 (Burr Decl. ¶¶ 45-50). In 2005, Merck received a report from an orthopedic surgeon of 25 patients who had taken Fosamax for "a long time" and suffered long bone fractures with features consistent with AFFs (although they were not specifically designated as AFFs), noting that in his hospital they call such a fracture the "Fosamax Fracture." J.A. 126-27 (Burr Decl. ¶ 52); J.A. 448. In 2006, a Merck employee in Singapore reported that she had learned of eight cases of atypical femoral fractures suffered by long-term Fosamax users and suggested that those events "might be a signal for a label update." J.A. 452, 455-56. As the Third Circuit summarized, "[b]etween 1995 and 2010, scores of case studies, reports and articles were published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures." Pet'r App.13a.

In June 2008, FDA sent Merck an information request titled: "Fosamax Information Request – Atypical Fractures." J.A. 280-81. FDA stated that it was "concerned about this developing safety signal" and it requested Merck to submit any investigations it had conducted "regarding the occurrence of atypical fractures with bisphosphonate use," any investigational

plans, and all hip and femoral fracture case reports that the company had received. *Id.* Shortly thereafter, Merck submitted the information FDA had requested. Pet'r App.14a.

Under the Federal Food, Drug and Cosmetic Act ("FDCA"), Merck could also have added a warning about atypical femoral fractures to its label in one of two ways. FDA's changes being effected ("CBE") regulation provides that when a manufacturer becomes aware of new information about serious adverse effects of a drug, it may revise its label to "'add or strengthen a contraindication, warning, precaution, or adverse reaction,' without waiting for FDA approval." *Wyeth v. Levine*, 555 U.S. 555, 569 (2009) (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)). Alternatively, the manufacturer may submit a prior approval supplement ("PAS") to FDA seeking a labeling change, which requires it to wait for FDA authorization prior to changing its labeling. 21 C.F.R. § 314.70(b).

Merck did not use either option to add a warning about atypical femoral fractures. Instead, in September 2008 it submitted prior approval supplements for each of its Fosamax products proposing to add language about "low-energy femoral shaft fracture," a broad category that includes AFFs and less serious fractures. J.A. 510-12. Specifically, the warning would have stated that: "[l]ow -energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma." There was no

mention in Merck's proposed warning of atypical femoral fractures. J.A. 707.

In May 2009, FDA sent a Complete Response Letter ("CRL") to Merck stating that the agency could not approve Merck's PAS applications "in their present form." J.A. 510-13. A complete response letter is the letter FDA sends when it has determined that it will not approve an application or a supplement to an application in its present form. 21 C.F.R. §§ 314.110(a), 314.71. FDA explained that "[w]hile the Division agrees that atypical and subtrochanteric fractures should be added to the Adverse Reactions, Post-Marketing Experience subsections of the . . . labels, your justification for the proposed Precautions section language is inadequate." J.A. 511 (capitalization and bold omitted).[2] According to FDA, "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been

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[2] Under FDA's regulations, there is a significant distinction between what is added in the Adverse Reactions/Post-Marketing Experience sections of the label and what is added to the Warnings and Precautions section. The Adverse Reactions/Post-Marketing Experience sections contain a laundry list of adverse reactions reported that are "reasonably associated with use of a drug." 21 C.F.R. § 201.57(c)(7). On the other hand, an addition to the Warnings and Precautions section must meet the higher standard of "reasonable evidence of a causal association between the drug and the adverse event." 21 C.F.R. § 201.57(c)(6). This section is "intended to identify and describe a discrete set of adverse reactions that are *serious* or are *otherwise clinically significant* because they have implications for prescribing decisions or for patient management." U.S. FOOD & DRUG ADMIN, WARNINGS, PRECAUTIONS, CONTRAINDICATIONS, AND BOXED WARNING SECTIONS OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS – CONTENT AND FORMAT: GUIDANCE FOR INDUSTRY 3 (2011).

reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting." J.A. 511-12. FDA informed Merck that it could "resubmit" its application. J.A. 512. In July 2009, Merck withdrew its PAS applications and added the approved femur fracture language only to the laundry list of Adverse Reactions in that section of the Fosamax label. J.A. 654-60. There was no mention of atypical femoral fractures. *Id.*

In rejecting Merck's application for a warning about stress fractures, FDA did not decide whether a warning about atypical femoral fractures was warranted. This issue was still under consideration as demonstrated by an email that an FDA employee had sent Merck just a month earlier. In that communication, FDA informed Merck that the Agency was interested in "work[ing] with . . . Merck to decide on language for a [Warnings and Precautions] atypical fracture language, if it is warranted." J.A. 508. There is no evidence that Merck ever followed up on FDA's invitation to work on a warning about atypical fractures or that it ever proposed such a warning to FDA. Nor did Merck exercise its authority under the CBE regulation to add a warning about atypical femoral fractures, which it could have done without awaiting FDA approval.

In 2009, the American Society for Bone and Mineral Research empaneled a task force (the "Task Force"), to address the issue of AFFs primarily in patients who had been taking bisphosphonates for a long period of time. J.A. 133. On September 14, 2010,

the Task Force published its report entitled "Atypical Subtrochanteric and Diaphyseal Femoral Fractures" (the "Task Force Report"). J.A. 283. The Task Force Report concluded that use of bisphosphonate, including Fosamax, increases the risk of atypical femoral fractures. *Id.* Less than a month later, on October 13, 2010, FDA announced that it would require bisphosphonate labeling to include a warning "describing the risk of atypical fractures of the thigh." J.A. 246. On that same day, FDA directed Merck to add three specifically worded paragraphs describing atypical femur fractures to the Warnings and Precautions section. J.A. 526-29.

Consistent with the PAS it had submitted two years earlier, Merck resisted the FDA drafted warning about atypical femoral fractures. Instead it proposed revised language that added five references to "stress fractures," including the language relating to risk factors for stress fractures that Merck had proposed and FDA had rejected in 2009. J.A. 606-07. FDA rejected each of Merck's proposed references to stress fractures and required a warning about atypical femoral fractures, explaining that "the term 'stress fracture' was considered and was not accepted" because, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use." J.A. 566.

ARGUMENT

Under the FDCA and FDA's implementing regulations, a drug manufacturer bears the responsibility for the content of its label at all times.

Wyeth v. Levine, 555 U.S. at 570-77; 21 C.F.R. § 201.56 (a)(2); 21 C.F.R. § 201.57(c)(6)(i); *see also* 21 U.S.C. § 355(o)(4)(I). FDA's regulations require a manufacturer to update its labeling "when new information becomes available that causes the label to become inaccurate, false or misleading." 21 C.F.R. § 201.56(a)(2). Updated warning information must be added "as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." 21 C.F.R. § 201.57(c)(6)(i). FDA relies on manufacturers to make label changes because "FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the post-marketing phase as new risks emerge." *Wyeth v. Levine*, 555 U.S. at 578-79.

Merck did not ask FDA to add a warning to the Fosamax label about atypical femoral fractures and FDA did not decide whether such a warning would be appropriate. Even if the Complete Response Letter that FDA issued in May 2009 had denied a request for a warning label about AFFs, and it did not, Merck was always free to resubmit its application (addressing the deficiencies identified by FDA in its CRL) or to ask for reconsideration by requesting a hearing on the question of whether there were grounds for denying the labeling change. 21 C.F.R. § 314.110(b). It also had the authority to use the CBE regulation and to add a warning about AFFs, which then FDA would have evaluated based on existing data or new analysis of that data.

I. Merck Did Not Request a Warning for Atypical Femoral Fractures.

In September 2008, Merck submitted a prior approval supplement proposing to add specific language to the Warnings and Precautions section of the Fosamax labeling. That language contained no reference to atypical femoral fractures. Instead the new warning language would have referred to "low-energy fractures of the subtrochanteric femoral shaft" (the upper part of the femur) and then it would have mentioned "stress fractures" six times. J.A. 707.[3] A low energy fracture is a broad term that encompasses a range of fractures, including both atypical femur fractures and stress fractures. J.A. 466; J.A. 109, 139 (Burr Decl.¶¶ 22,73). The term "low energy fracture" is not a red flag because

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[3] The full text of the proposed warning was as follows:

Low-Energy Femoral Shaft Fracture

Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area *often* associated with imaging features of stress fracture weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonate. Patients with suspected stress fractures should be evaluated including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse) and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered pending evaluation of the patient, based on individual benefit/risk assessment.

some low energy fractures, such as stress fractures, are relatively common and less medically significant than others, including AFFs. J.A. 139-41 (Burr Decl. ¶¶ 73-75.) Thus, this term does not specifically identify AFFs and the proposed language was not a warning for this very serious type of fracture.

A stress fracture is "an incomplete fracture of a long bone," the vast majority of which "never progress to a full and complete fracture," and which is generally treated "by prescribing rest or inactivity in the affected bone." J.A. 144 (Burr Decl. ¶ 83). By contrast, atypical femoral fractures often progress to a "completed subtrochanteric fracture" of the femur and are "much more significant than 'garden-variety' stress fractures, which usually heal uneventfully with simple rest and without full fracture." J.A. 145-46 (*id.* ¶ 86). As FDA explained in an email rejecting Merck's proposed changes to its 2010 warning, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use." J.A. 566. Merck itself has recognized that "most of the stress fractures general physicians have seen are associated with repetitive stress injury related to exercise (e.g., running) in younger adults, and that this type of stress fracture generally heals well with rest." Ct. Appeal App.1573.

According to Dr. David Burr, a co-chair of the Task Force and one of the primary authors of the Task Force Report, Merck's proposed warning "improperly conflated the underlying fracture mechanism that leads to AFFs with the ultimate outcome." J.A. 144 (Burr Decl. ¶ 84). Merck's proposed warning also

conflated the rare type of stress fracture that can develop into AFFs with typical stress fractures. According to Dr. Burr, Merck's proposed warning listed "risk factors" for stress fractures that "simply were not associated with AFF," including "extreme or increased exercise." J.A. 142 (Burr Decl. ¶ 79); J.A. 707. In other words, "Merck was attempting to confound the true nature of the association between Fosamax and AFFs." J.A. 143 (Burr Decl. ¶ 81).

Although Merck requested a warning about stress fractures, which FDA concluded was not supported by available data, it never attempted to add a warning for AFFs.

II. The Complete Response Letter Demonstrates that FDA Did Not Reject a Warning for AFFs.

In May 2009, Dr. Scott Monroe, the Director of the FDA Division of Bone, Reproductive and Urologic Products, sent the Division's decision, or Complete Response Letter, to Merck, rejecting its proposal to warn of femur fractures that Merck referred to as "low energy femoral shaft fractures" and "stress fractures." In the CRL, Dr. Monroe explained that "[w]hile the Division agrees that atypical and subtrochanteric fractures should be added to the Adverse Reactions, Post-Marketing Experience subsections of the . . . labels, your justification for the proposed precautions section language is inadequate." J.A. 511. (Capitalization and bold omitted.) According to Dr. Monroe, "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." *Id.* "Discussion of the risk factors for stress fractures is not warranted and is not

adequately supported by the available literature and post-marketing adverse event reporting." J.A. 511-12.

In other words, FDA rejected Merck's request to add a Warning about stress fractures. It could not and did not reject a warning regarding AFFs, because Merck had never asked for one. Nothing in the Complete Response Letter supports what Merck and the Solicitor General contend was the reason behind FDA's decision: a finding by FDA that there was a lack of scientific evidence that Fosamax caused atypical femoral fractures. *See* Pet'r Br. at 49; Solicitor Gen. Br. at 30-31.

A close examination of the CRL demonstrates the flaws in Merck and the Solicitor General's argument. The first sentence of the CRL states that Merck's "justification" for its "proposed ... language is inadequate." The next sentence explains that the justification for Merck's language was inadequate because "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." In other words, FDA had been concerned about atypical femoral fractures reported in the literature. Rather than request permission to give a warning about those fractures, Merck had sought a warning about stress fractures, for which FDA found that there was insufficient literature support. Again, the CRL did not state that there was insufficient evidence to support an association between Fosamax and atypical femoral fractures. According to the CRL, the only thing that was "not adequately supported" was "[d]iscussion of the risk factors for stress fractures." FDA's conclusion was consistent with the subsequent findings of the ASMBR Task Force that "many of the 'risk factors' identified by

Merck in its submission to the FDA simply were not associated with AFF." J.A. 142 (Burr Decl. ¶ 79).

FDA's issuance of the CRL denying Merck's request for a warning about stress fractures in May 2009 complied with the decision date for responses to PASs established under the Prescription Drug User Fee Act.[4] On the other hand, there was no decision date for deciding on a warning about AFFs because Merck had not submitted a PAS requesting such a warning, and FDA often takes a long time to resolve this type of issue. That FDA had not decided whether a warning about AFFs would be appropriate is confirmed by an April 15, 2009 email from Karl Stiller, FDA Regulatory Project Manager, Division of Bone, Reproductive and Urologic Products, to Merck, regarding a recent discussion that Merck had had with Dr. Monroe (the author of the CRL) and Dr. Kehoe, a Medical Officer and Team Leader in the Division. The email stated that FDA was interested in "work[ing] with ... Merck to decide on language for [Warnings and Precautions] atypical fracture language, if it is warranted." J.A. 508. Written just a month before the CRL, and probably at a time when the substance of the CRL had been decided, this email was an invitation to Merck to work with FDA to agree on language that warned about AFFs.

The Solicitor General states in one of the headings in his brief that "FDA's May 2009 Decision

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[4] U.S. FOOD & DRUG ADMIN., FY 2008 PERFORMANCE REPORT TO THE PRESIDENT AND THE CONGRESS FOR THE PRESCRIPTION DRUG USER FEE ACT (2008), https://wayback.archive-it.org/7993/20170113075401/http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM209479.pdf.

Rejected A Change To Fosamax's Warnings And Precautions Because The Data At That Time Was Insufficient To Justify A Change." Solicitor Gen. Br. at 30 (capitalization in original). He then asserts that "FDA's May 2009 decision rejecting petitioner's proposal to modify Fosamax's Warnings and Precautions section to address atypical femoral fractures was based on the agency's determination that the information about that risk was then insufficient to justify such a warning." *Id.* Both these statements are rebutted by the warning that Merck actually proposed which mentioned stress fractures six times but did not contain a single reference to AFF. *See supra* p. 9 n.3. As the email from the FDA official to Merck demonstrates, FDA had not decided the AFF issue and had attempted to work with Merck on a warning about AFFs if one was warranted.

In October 2010, following publication of the Task Force Report, FDA required Merck to add a warning on Fosamax labeling about the risk of atypical femoral fractures. When FDA offered Merck the opportunity to comment on the warning about AFFs, Merck proposed revised language that added five references to "stress fractures," including the language relating to risk factors for stress fractures that Merck had proposed and FDA had rejected in 2009. J.A. 606-07. FDA sent Merck a redline striking out each reference to stress fractures. *Id.*

In their response to FDA, Merck's representatives acknowledged that "most of the stress fractures general physicians have seen are associated with repetitive stress injury related to exercise (e.g., running) in younger adults, and that this type of stress

fracture generally heals well with rest." Ct. Appeal App.1573. As Dr. Burr explained, atypical femoral fractures often progress to a "completed subtrochanteric fracture" of the femur and are "much more significant than 'garden-variety' stress fractures, which usually heal uneventfully with simple rest and without full fracture." J.A. 145-46 (Burr Decl. ¶ 86).

The text of the CRL demonstrates that it was not, as Merck contends, a "flat ... rejection" of any femur fracture warning. Pet'r Br. at 34. In fact, FDA stated: "we cannot approve these applications *in their present form*." J.A. 511 (emphasis added). FDA invited Merck "to resubmit" its application and to call an FDA regulatory project manager with any questions, J.A. 512-13, and it had previously informed Merck that it would like to work with the company on crafting a warning about AFFs. Thus, the CRL did not preclude Merck from adding an adequate warning of atypical femoral fractures through resubmission of its PAS. Nor did it preclude Merck from adding an AFF warning via the CBE process, after which FDA would have decided whether it was supported by the data. Merck did neither.

III. Merck Could Have Added a Warning about AFFs Between May 2009 and September 2010 or Submitted a PAS Requesting that FDA Approve a Warning.

As discussed at page 3, *supra*, Merck started to receive adverse event reports suggesting problems with AFFs long before it submitted its PAS application in 2009. In June 2005, Merck performed an internal statistical analysis of Fosamax adverse event reports

and concluded that, as early as 2003, these reports revealed a statistically significant incidence of femur fractures. Ct. Appeal App. 1272-73, 1407, 1443. Respondents' expert biostatistician, David Madigan, confirmed that in 2005 FDA's adverse event database for Fosamax showed a statistically significant signal of a relationship between Fosamax and femur fractures. J.A. 189-92. In 2006, a Merck employee reported that she had learned of femoral fractures suffered by long-term Fosamax users and suggested that those events "might be a signal for a label update." J.A. 452, 455-56.

Likewise, numerous published scientific studies documented the connection between bisphosphonates and atypical femoral fractures. For example, a 2004 article discussed several Fosamax patients who had suffered atypical femoral fractures and concluded that "[o]ur findings raise the possibility that severe suppression of bone turnover may develop during long-term alendronate therapy, resulting in increased susceptibility to, and delayed healing of, non-spinal fractures." J.A. 416. A 2008 article published a study of 25 Fosamax users who had suffered atypical femoral fractures, concluding that such fractures were "associated with alendronate use." J.A. 385.

Dr. David Burr, the co-chair of the Task Force, which issued the 2010 report, has confirmed that the Task Force did not conduct any additional research; it based its report on its "review" of "the currently available information," most of which was "available before May of 2009". J.A. 133-34 (Burr Decl. ¶¶ 62, 64). Specifically, the Report summarized what was known at the time about the relationship between bisphosphonates and atypical femoral fractures. Of

the 37 published cases reported and relied on by the task force, 19 were available to Merck by the time it submitted its PAS applications in May 2009. Of the 177 published or available articles and posters cited by the Task Force Report, 120 were available before 2009. J.A. 134 (Burr Decl.¶ 64).

Finally, the fact that FDA mandated an atypical femoral fracture warning soon after the Task Force Report accurately described the fractures suggests that Merck could have added an accurate atypical femoral fracture warning much earlier. As recounted in the Solicitor General's brief, after FDA announced that it was requiring a warning about AFFs on Fosamax and other bisphosphonates, "FDA's Deputy Director for the Office of New Drugs explained that the data that FDA had previously reviewed was insufficient to allow the agency to 'tease out the association between [Fosamax and similar products] and these rare atypical fractures,' but that the task force's September 2010 report had helped FDA 'understand the[] fractures' better." Solicitor Gen. Br. at 11. The FDA official also stated that the Task Force Report "helped . . . make us confident that this is something that is potentially more closely related to these drugs, particularly long-term use than we previously had evidence for." J.A. 494.

As previously noted, FDA relies on manufacturers to make label changes because "FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the post-marketing phase as new risks emerge." *Wyeth v. Levine*, 555 U.S. at 578-79. Merck had access to most

of the data and studies that the Task Force used in its analysis and thus could have applied the analysis used by the Task Force to assist FDA in understanding the data on AFFs. In other words, Merck could have resubmitted its PAS (as FDA suggested) or submitted a CBE and changed its label even sooner. As discussed below, there is no evidence that FDA would have rejected a properly worded warning about AFFs.

IV. Even If FDA Had Rejected a Request by Merck to Warn of the Risk of AFFs, the Task Force Report and FDA's Response Demonstrate that with Appropriate Analysis of Existing Data Merck Could Have Added a Warning about AFF.

FDA's October 2010 decision to require bisphosphonate manufacturers to add an atypical femoral fracture warning after the Task Force had submitted its report demonstrates that Merck likely would have been successful had it in 2009 resubmitted its PAS or unilaterally added an adequate warning. FDA's actions prior to that time also support the conclusion that it would not have rejected a properly worded warning.

In March 2010, following news reports about the risk of AFFs in patients using bisphosphonates, FDA announced that it was "working closely with outside experts, including members of the recently convened [ASBMR] Task Force, to gather additional information." J.A. 519-20.[5] On September 14, 2010, just one month

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[5] Merck notes that FDA stated that "the data . . . reviewed have not shown a clear connection between bisphosphonates . . .

after the Task Force published its report, FDA announced that the Task Force's "case definition that describes the atypical features of these unusual femur fractures," would "help greatly" in identifying cases and understanding the risk. J.A. 523. FDA noted that it was considering the Task Force's recommendation that product labels alert health care professionals to the possibility of AFF. J.A. 524. Just one month later, on October 13, 2010, FDA directed bisphosphonate manufacturers to include information about atypical femoral fractures in the Warnings and Precautions section. J.A. 246. FDA noted that the Task Force Report summarized data regarding bisphosphonates and atypical subtrochanteric and diaphyseal femur fractures. J.A. 249.[6]

In a media call on that same day, FDA's Deputy Director for the Office of New Drugs explained that the report "helped us understand these fractures a little bit better," J.A. 494, and "helped to clarify the features of atypical femur fractures." J.A. 488. All of these pronouncements demonstrate that FDA did not view the Task Force Report as providing new data connecting

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and . . . atypical femoral fractures." Pet'r Brief at 13; J.A. 519. The standard for adding a warning, however is not a "clear connection" but rather "as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." 21 C.F.R. § 201.57(c)(6)(i). It was at this point that Merck was obligated to change its labeling. Indeed, even when FDA mandated a warning in October 2010, it stated that it was "not clear if bisphosphonates are the cause" of atypical femoral fractures. J.A. 247.

[6] Dr. Burr, co-chair of the Task Force and a principal author of the report, confirmed that the report presented no new data but merely reviewed and reported on "the currently available information" regarding atypical femoral fractures. J.A. 133-34.

bisphosphonates to atypical femoral fractures but rather a summary of existing data that "clarif[ied] the features of atypical femur fractures", and this clarification was sufficient to lead FDA to mandate a warning. J.A. 249, 488. As described above, Merck had access to that same data, and Merck could have assisted FDA in understanding the data, but instead Merck submitted a prior approval supplement that sought to warn about stress fractures instead of the fractures that FDA had been concerned about, AFFs.

Finally, Merck's acquiescence to FDA's demand to add a label removes any doubt about the current state of the science. *See* J.A. 223-24. Merck, respondents, and FDA all agree that in 2010 there was reasonable evidence of a causal association between Fosamax and atypical femoral fractures. As described above, almost all of the evidence available in 2010, and certainly more than enough of that evidence to support a warning, was available to Merck long before FDA demanded a labeling change.

Merck's position is not, as Merck contends, supported by *Pliva v. Mensing*, 564 U.S. 604 (2011). Pet'r Br. at 28-29. In *Mensing*, the plaintiffs argued that a generic drug manufacturer's failure to warn about a severe neurological disorder associated with use of the drug violated the manufacturer's state law obligation to provide such a warning. 564 U.S. at 609. As the Court pointed out, generic drug manufacturers cannot use the PAS or CBE process that is available to brand name manufacturers. *Id.* at 613. Their labeling "must be the same as" the brand name's labeling. *Id.* As a result, this Court held that it was "impossible" for

the generic drug manufacturer to comply with the state and federal law. *Id.* at 618-19.[7]

The facts of this case, however, do closely track the interactions between the drug manufacturer and the FDA described by the Supreme Court in *Wyeth v. Levine*. Wyeth argued that Levine's failure-to-warn claims were preempted because Wyeth had proposed warning language regarding the risk of intravenous injection of Phenergan, and "FDA rejected Wyeth's proposal." *Wyeth v. Levine*, 555 U.S. at 605 n.1 (Alito, J., dissenting). Although Wyeth's proposed warning addressed intravenous injection generally, it did not warn adequately of the specific dangers of using the IV-push method. *Id.* at 572 & n.5 (majority opinion). This Court therefore rejected Wyeth's argument because Wyeth had not "attempted to give the kind of warning required by the Vermont jury." *Id.* at 572. The Court held that "absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements." *Wyeth v. Levine*, 555 U.S. at 571.

Thus, unlike *Pliva*, Merck could have changed its labeling without violating federal law. All Merck had to do was to use the available information to either ask FDA to approve a resubmitted PAS or to use the CBE

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[7] Nor does *Mutual Pharm. Co. v. Bartlett*, 570 U.S. 472 (2013), support Merck. In *Bartlett*, the Court rejected plaintiffs' argument that there was no preemption even if the generic manufacturer could have complied with federal and state law by taking its product off of the market. Merck was not faced with this choice because, unlike the generic manufacturers in *Mensing* and *Bartlett*, it had the authority to revise its label.

process to unilaterally change its label without awaiting FDA approval. Nonetheless, Merck did neither.

CONCLUSION

A critical question in this case is whether FDA would have permitted Merck to warn about AFFs prior to the Task Force Report. The Solicitor General and Merck's position that FDA rejected its warning for AFFs is rebutted by the fact that Merck never asked for a warning for AFFs. Instead Merck asked for a warning on stress fractures, and in its complete response letter FDA rejected that request. FDA made it perfectly clear, both in the letter and in a communication that preceded the letter's issuance, that it had not decided on whether to require a warning about AFFs. Thus, under FDA's regulations, Merck could have added a warning about AFFs after giving FDA 30-days' notice of its intent to do so. Since the record shows that FDA had not decided whether a warning about AFFs was appropriate, it would have been consistent with FDA practice to allow Merck to add the warning while the agency was studying the issue.

FDA immediately ordered Merck to add the warning once the Task Force "helped [FDA] understand these fractures" and "clarif[ied] the features of atypical femur fractures." *See supra* p. 19. Merck could have obtained a decision from FDA approving a warning about AFFs in 2009 or earlier if it had offered FDA the analysis that the Task Force provided. Instead Merck chose to obfuscate the true nature of AFFs by focusing its PAS on stress fractures.

A decision preempting respondents' claims here would give pharmaceutical manufacturers an incentive to request permission to add a warning that is not supported by scientific data and then to use FDA's decision rejecting that request as a basis for obtaining preemption of a claim that the manufacturer should have added a related warning that was supported by scientific data. Such a decision would be entirely inconsistent with previous decisions of this Court.

Accordingly, the opinion of the Third Circuit should be affirmed.

RESPECTFULLY submitted.

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IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,

Petitioner,

v.

DORIS ALBRECHT, ET AL.,

Respondents.

On Writ of Certiorari to the
United States Court of Appeals for the Third Circuit

BRIEF OF AMICI CURIAE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA AND BIOTECHNOLOGY INNOVATION ORGANIZATION IN SUPPORT OF PETITIONER

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INTEREST OF AMICI CURIAE

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary nonprofit association representing the country's leading research-based pharmaceutical and biotechnology companies.[1] PhRMA advocates in support of public policies that encourage the discovery of life-saving and life-enhancing new medicines. PhRMA members produce innovative medicines, treatments, and vaccines that save and improve the lives of countless individuals every day. PhRMA members have invested more than half a trillion dollars in R&D since 2000, and in 2017 alone invested an estimated $71.4 billion in discovering and developing new medicines. PhRMA, *Biopharmaceuticals in Perspective: Spring 2017*, at 35 (2017), http://phrma-docs.phrma.org/files/dmfile/Biopharmaceuticals-in-Perspective-2017.pdf [hereinafter *Biopharmaceuticals in Perspective*]; *About*, PhRMA, https://www.phrma.org/about#key (last visited September 17, 2018).

The Biotechnology Innovation Organization ("BIO") is the world's largest biotechnology

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[1] Pursuant to Rule 37.6, *amici* affirm that no counsel for a party authored this brief in whole or in part and that no person other than *amici*, their members, or their counsel made any monetary contributions intended to fund the preparation or submission of this brief. A list of PhRMA members is available at http://www.phrma.org/about/members. A list of BIO members is available at https://www.bio.org/bio-member-directory. Merck & Co. is a member of PhRMA, but did not contribute financially to the preparation of this brief. The parties have consented in writing to the filing of all timely *amicus* briefs.

organization, providing advocacy, business developments, and communications services for its members worldwide. BIO's mission is to champion biotechnology and advocate for its member organizations, both large and small. BIO members are involved in research and development of innovative healthcare technologies, and corporate members range from entrepreneurial companies developing a first product to Fortune 500 multinationals. BIO also represents state and regional biotechnology associations, service providers to the industry, and academic centers.

This case presents a question of critical importance for members of PhRMA and BIO: whether, after the Food and Drug Administration ("FDA") considers a potential safety issue but ultimately decides after reviewing the relevant scientific data that no warning is justified, a jury may nonetheless hold the company liable under state law for failing to provide the warning the FDA rejected. The burdens of product liability litigation are already substantial for life sciences companies, and a regime that permits these companies to be held liable under state law for failure to include warnings expressly deemed inappropriate or unwarranted by the FDA would greatly compound that liability in a manner that both is unfair and could deter innovation. The Court should reverse the Third Circuit's judgment and establish clear, consistent, and fair preemption rules for FDA-rejected warnings.

INTRODUCTION AND SUMMARY OF ARGUMENT

The FDA brings its extensive scientific expertise to bear in approving medically-appropriate labeling for prescription medicines, both before and after they are brought to market. Congress granted the FDA authority to review and approve labeling in recognition of the agency's institutional capacity to assess how best to communicate complex risk and benefit information, including evaluating the scientific basis for proposed warnings. In *Wyeth v. Levine*, 555 U.S. 555 (2009), this Court considered the FDA's role and held that state-law tort claims are preempted when it is clear that the FDA would have rejected the labeling that a plaintiff asserts was required by state law.

After the events at issue in *Levine*, Congress gave the FDA additional authority over labeling in the Food and Drug Administration Amendments Act of 2007 ("FDAAA"), Pub. L. No. 110–85, 121 Stat. 823. The FDAAA adopted Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act ("Section 505(o)(4)"), codified at 21 U.S.C. § 355(o)(4), which *requires* the FDA to add safety information to a medicine's labeling when the agency recognizes a new serious safety risk, and grants the FDA express authority to require such labeling changes. Under Section 505(o)(4), when the FDA becomes aware of a new serious safety issue that it determines should be reflected in labeling, the FDA *must* engage with a drug's sponsor to add appropriate labeling. Neither quibbles over language nor sponsor recalcitrance can stand in the way of updating the

label to reflect this new safety information. Under the revised statutory regime, when the FDA has considered a potential new safety issue and exercised its scientific judgment to conclude that no new labeling is required, the agency's decision not to adopt such labeling provides dispositive evidence that the FDA would have rejected *any* warning for that particular safety risk, regardless of the language used.

The FDA's new affirmative obligations under Section 505(o)(4) thus modify the preemption equation presented in *Levine*. *Levine* focused on a sponsor's duty to update labeling unilaterally under the FDA's "Changes Being Effected" regulations, and left open the possibility that the FDA might have accepted a sponsor's proposal to amend its warning in a manner that subsequent litigation adversaries argue was required by state law. In this case, however, after considering the available scientific evidence addressing the potential new serious safety issue, the FDA rejected Merck's proposal to include such a warning. There is no basis for thinking that the FDA's decision was driven by dissatisfaction with the specific language of Merck's proposal. If the FDA had believed that the safety issue needed to be reflected in the label, it was under a statutory obligation to propose alternative language to address that safety issue. The FDA's flat rejection was not accompanied by any counter-proposal, and thus reflected the agency's considered judgment that no additional labeling was justified. Unlike the pre-Section 505(o)(4) situation in *Levine*, the FDA's decision not to adopt the proposed labeling constitutes

precisely the "clear" rejection that the Court envisioned in *Levine*.

The Third Circuit disagreed, holding that preemption of state-law claims is a factual determination reserved for jury resolution absent a "'smoking gun' rejection letter" laying out the FDA's rationale for rejecting the warnings sought. Pet. App. 55. The Third Circuit's approach cannot be reconciled with the FDA's statutory duties under the FDAAA. The Third Circuit's preemption standard will also hinder the FDA's ability to ensure that labeling contains essential, scientifically-based information, and it will give manufacturers an incentive to inundate the FDA with linguistic variants of labeling requests in an effort to attain a level of clarity sufficient to trigger preemption. In addition, the regime endorsed by the Third Circuit could discourage innovation and pose a threat to public health.

Section 505(o)(4) now requires that the FDA must act whenever it identifies a new potential serious safety issue, and this Court should clarify that the Third Circuit's preemption analysis cannot be reconciled with the current federal regulatory regime. The decision of the Third Circuit should be reversed.

ARGUMENT

I. The FDAAA Materially Affects the *Levine* Preemption Calculus.

Given the statutory framework in which the FDA and drug manufacturers operate, the Third Circuit erred in its interpretation and application of *Wyeth v. Levine*. The Third Circuit's decision does not take proper account of the complexities of drug labeling or the obligations of the FDA and manufacturers throughout the labeling process, particularly following the enactment of the FDAAA and the FDA's duty to amend a drug's labeling if it identifies an unlabeled serious safety risk that requires a warning. 21 U.S.C. § 355(o)(4). In light of that affirmative statutory obligation, where the FDA considers a potential new safety issue but ultimately concludes that the new safety information does not warrant new labeling, that regulatory decision necessarily provides the requisite verification that the FDA would have rejected a labeling proposal from a sponsor containing such information. In this case, the situation is even more stark, because the FDA expressly rejected Merck's specific request for such labeling. Because Section 505(o)(4) places a duty on the FDA to amend labeling if it deems it necessary once presented with a potential serious safety issue, it is no answer to say Merck did not use the right words or did not press hard enough for the change. Because the FDA rejected Merck's proposed labeling without pursuing additional communications regarding labeling language, the FDA's rejection was necessarily grounded in science, not in language quibbles.

A. The Current Statutory Regime Governing Labeling for Prescription Medicines.

1. The FDA Is the Final Arbiter of the Contents of a Medicine's Labeling.

To ensure that "the public get[s] the accurate, science-based information they need," the FDA tightly regulates the labeling for all prescription medicines. *What We Do*, FDA, https://www.fda.gov/aboutfda/whatwedo/default.htm# mission (last updated Mar. 28, 2018). FDA regulations set out detailed labeling requirements, specifying required categories, precise information each category should include, and, in many cases, exact formatting standards. *See* 21 C.F.R. §§ 201.56-57, 201.66, 201.80. As relevant here, medicine labeling must warn about any serious hazard for which there is "reasonable evidence of a causal association." 21 C.F.R. § 201.57(c)(6).

The FDA must approve labeling before a medicine can be marketed, and the agency continues to scrutinize labeling for as long as the medicine remains on the market. While the manufacturer bears responsibility for its labeling, the FDA is the final authority on its contents. Before a manufacturer can amend its labeling, it generally must obtain FDA approval through the submission of a "prior approval supplement" ("PAS") to its New Drug Application. *See* 21 C.F.R. § 314.70(b)(2)(v). Manufacturers can, in some circumstances, add or strengthen a warning to reflect "newly acquired information." *See id.*

§ 314.70(c)(6)(iii). Even then, however, a manufacturer cannot distribute the new labeling until it submits a "changes being effected" ("CBE") supplement to the FDA. *See id.* § 314.70(c)(3)–(6). Once a CBE supplement is submitted, the FDA must review the contents of the amended labeling, and if the FDA does not find that "the evidence of a causal association satisfies the standard for inclusion in the labeling," *id.* § 314.70(c)(6)(iii)(A), it must retroactively reject the change and may order the manufacturer to stop distributing products with the new labeling, *see id.* § 314.70(c)(6)–(7); Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49,603, 49,608 (Aug. 22, 2008) ("[A] CBE supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug . . . ."). In all circumstances, then, the FDA is the final arbiter of the contents of new and amended drug labeling.

In exercising its authority, the FDA frequently communicates with drug manufacturers regarding new and amended labeling. As the Solicitor General's brief confirms, the FDA engages with manufacturers with regard to "scientific, medical, and procedural issues that arise" throughout the "iterative" labeling process. U.S. Cert. Br. at 5 (citations omitted). Notably, the FDA may communicate with manufacturers to address "minor" or "editorial" issues involved in proposed labeling:

> If FDA reviewers identify "easily correctable deficiencies" in a supplement, they will "make every reasonable effort to communicate [them] promptly to applicants." 21 C.F.R. 314.102(b). And if only "editorial or similar minor deficiencies in the [proposed] labeling" exist, FDA may approve the supplement on the condition that the applicant makes appropriate corrections and submits a copy of the final labeling before marketing the drug with that labeling. 21 C.F.R. 314.105(b).

Id. at 5–6. The dynamics of the FDA-manufacturer relationship thus involve frequent communications throughout a tightly-regulated labeling process.

2. The FDA Now Has an Affirmative Duty to Amend Labeling When It Concludes New Safety Information Should Be Conveyed.

The FDA's role in medicine labeling includes a duty to ensure labeling remains adequate after medicines are marketed. If the FDA becomes aware of a safety concern that requires a warning — either from a manufacturer's submission or through the FDA's own continuous monitoring of adverse event

reports[2] — the FDA must ensure the necessary labeling changes are adopted.

Legislative changes enacted in 2007 expanded the FDA's authority and affirmative obligation to amend labeling. Once the FDA "becomes aware of new safety information that [it] believes should be included in the labeling of the drug," Section 505(o)(4) requires the FDA to "promptly" engage the drug's sponsor to amend the drug's labeling. *See* 21 U.S.C. § 355(o)(4)(A).[3] In its notification, the FDA details the source of the new safety information, a description of the safety information, proposed labeling changes, and instructions for the manufacturer. *See FDA Guidance for Industry*, *supra*, at 6.[4]

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[2] Manufacturers are required to report "serious and unexpected" adverse events to the FDA within 15 days of receipt and to periodically report all other adverse events. 21 C.F.R. § 314.80. The FDA also receives adverse event reports through a voluntary reporting system, *MedWatch: The FDA Safety Information and Adverse Event Reporting Program*, FDA, https://www.fda.gov/Safety/MedWatch/default.htm (last updated Aug. 29, 2018).

[3] The FDA has compiled a non-exhaustive list of sources of new safety information in guidance it issued regarding Section 505(o)(4). *See Guidance for Industry: Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act*, FDA (July 2013) at 16, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf [hereinafter "*FDA Guidance for Industry*"].

[4] Notification letters that apply to a single manufacturer "are considered confidential commercial information and are not posted" on the FDA's website. The "resulting supplement is

After receiving a notification letter, a manufacturer must submit a "supplement proposing changes to the approved labeling to reflect the new safety information," or notify the FDA that it "does not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted." *See* 21 U.S.C. § 355(o)(4)(B). After receiving a manufacturer's response, Section 505(o)(4) requires the FDA to:

> promptly review and act upon such supplement. If the [FDA] disagrees with the proposed changes in the supplement or with the statement setting forth the reasons why no labeling change is necessary, the [FDA] shall initiate discussions to reach an agreement on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes.

See id. § 355(o)(4)(C).

Section 505(o)(4) also grants the FDA express authority to "issue an order directing the [manufacturer] to make such a labeling change as the [FDA] deems appropriate to address the new safety information." *See id.* § 355(o)(4)(E). Following such an order, a manufacturer is required to submit labeling changes within 15 days. *See id.*

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approved and posted," however. *See FDA Guidance for Industry*, *supra*, at 13.

§ 355(o)(4)(E). Section 505(o)(4) gives the FDA authority to "accelerate the timelines" where it "concludes that such a labeling change is necessary to protect the public health." *See id.* § 355(o)(4)(H).

The FDAAA thus marked a significant increase in the FDA's authority and responsibility to ensure a medicine's labeling remains scientifically accurate during its marketing. To be sure, prior to 2007 the FDA possessed considerable practical ability to generate labeling changes through its authority to (1) withdraw approval of a medicine if its labeling was "false or misleading in any particular," 21 U.S.C. § 355(e), and (2) bring an enforcement action against the manufacturer for misbranding, *see id.* § 352(a). Under the former statutory scheme, however, the FDA lacked express statutory authority to order a labeling change after the approval of a medicine. *See Levine*, 555 U.S. at 571 ("Indeed, prior to 2007, the FDA lacked the authority to order manufacturers to revise their labels."). Following enactment of the FDAAA, the FDA has both the authority and the *affirmative duty* to add safety information to labeling to address an unlabeled safety concern.

The legislative record surrounding the FDAAA reflects Congress's intent to increase the FDA's authority and responsibilities in order to better protect public health. *See, e.g.*, 153 Cong. Rec. S10136–37 (daily ed. July 26, 2007) (statement of Sen. Grassley). The House report notes that the FDAAA "strengthens FDA's postmarket drug safety authority" by "provid[ing] FDA with the authority to require labeling changes under appropriate

circumstances." H.R. Rep. No. 110–225, at 4 (2007). Moreover, Senator Grassley, a co-sponsor of the bill, noted, "[Congress] need[ed] to make sure that we're giving FDA, the watchdog, some bite to go with the bark." 153 Cong. Rec. S10137 (daily ed. July 26, 2007) (statement of Sen. Grassley). A bipartisan group of lawmakers observed that once the FDA has identified potential safety issues, it "needs to be empowered . . . to take action to address those questions and to ensure timely notice to doctors and consumers of new safety risks that they are already taking." 153 Cong. Rec. S5628 (daily ed. May 7, 2007) (statement of Sen. Grassley); 153 Cong. Rec. S11832 (daily ed. Sept. 20, 2007) (statement of Sen. Kennedy) ("This legislation will give FDA the authority, for the first time, to compel a drug company to add warnings of newly discovered risks on the drug label."); 153 Cong. Rec. S11835 (daily ed. Sept. 20, 2007) (statement of Sen. Durbin) (noting "[t]he bill gives the FDA more tools to detect the safety problems of drugs after they are available to consumers[]" and "the FDA is given greater authority to require drug companies to add warning labels[.]").

Indeed, the FDAAA reflected both an effort to strengthen the FDA's authority and responsibility to oversee labeling and to confirm that manufacturers retain responsibility if they fail to update their labeling with new safety information. *See* 21 U.S.C. § 355(o)(4)(I) ("This paragraph shall not be construed to affect the responsibility of the [sponsor] to maintain its label in accordance with existing requirements [including the CBE regulations]"); *see also Levine*, 555 U.S. at 567–68 (citing 121 Stat. 925–926) (noting that

Congress "adopted a rule of construction to make it clear that manufacturers remain responsible for updating their labels"). The legislative history of the FDAAA confirms these joint goals. *See* 153 Cong. Rec. S11839–40 (daily ed. Sept. 20, 2007) (statement of Sen. Coburn) (noting "the newly expanded role of the FDA does and should preempt State law when it comes to drug safety and labeling," and maintaining that long-standing preemption principles remain following the FDAAA "because there is an overriding Federal interest in ensuring that the FDA, as the public health body charged with making these complex and difficult scientific judgments, be the final arbiter of how safety information is conveyed."); *see also* 153 Cong. Rec. S11832 (daily ed. Sept. 20, 2007) (statement of Sen. Kennedy) (noting that "[b]y enacting this legislation, we do not intend to alter existing state law duties imposed on a drug manufacturer to obtain and disclose information regarding drug safety hazards either before or after a drug receives FDA approval or labeling," but also stating, "[w]e do not believe that the regulatory scheme embodied in this act is *comprehensive enough to preempt the field or every aspect of state law.*") (emphasis added). Thus, while manufacturers retain responsibility for labeling, the FDAAA unmistakably increased the FDA's authority to change labeling. Accordingly, the FDAAA marked a meaningful change to the FDA's obligations and authority.

B. The FDA's Additional Statutory Obligations Under the FDAAA Materially Affect the Preemption Analysis Where the FDA Expressly Considers the Safety Information at Issue.

Because the FDAAA was enacted after the events in *Levine*, this Court did not consider the effect of that statute on the preemption analysis. *See Levine*, 555 U.S. at 567 (citation omitted) ("In 2007, after Levine's injury and lawsuit, Congress again amended the FDCA. For the first time, it granted the FDA statutory authority to require a manufacturer to change its drug label based on safety information that becomes available after a drug's initial approval."). The Court held in *Levine* that if "the FDA would not have approved" a label required by state law, then the state law claim would be preempted. *Id.* at 571. In *Levine*, the Court held that Wyeth had presented no "clear evidence" that the FDA would not have approved a change to Phenergan's label and emphasized that the FDA had never given "more than passing attention" to the safety issue alleged in the lawsuit. *Id.* at 571–72.

In this case, the Third Circuit, interpreting *Levine*, held that preemption is a factual determination reserved for jury resolution absent a "'smoking gun' rejection letter" laying out the FDA's rationale for rejecting the warnings sought. Pet. App. 55. The Third Circuit's conclusion does not take

proper account of the FDA's affirmative obligations under the FDAAA.

As explained above, where the FDA has determined, considering the scientifically-based evidence at its disposal, that new safety information warrants a warning, it has an affirmative duty to add information to the labeling about that risk using Section 505(o)(4). Under Section 505(o)(4), the FDA may take one of three paths when it has determined that an unlabeled safety risk should be reflected in labeling. First, a manufacturer may submit proposed labeling in response to the FDA's notification that amended labeling is required. 21 U.S.C. § 355(o)(4)(B). The FDA is then required to act on the manufacturer's proposal, and either accept the proposed labeling or work with the manufacturer to determine the contents of the labeling through an iterative process. *Id.* § 355(o)(4)(C). Second, the manufacturer may disagree that a labeling change is necessary. *Id.* § 355(o)(4)(B). In that case, the FDA must continue to work with the manufacturer to reach agreement as to the necessity of a labeling change, and, if the FDA still feels a labeling change is required, to determine the contents of the labeling. *Id.* § 355(o)(4)(C). Third, if cooperative efforts between the FDA and the manufacturer are not successful, the FDA may issue an order compelling the manufacturer to submit labeling changes. *Id.* § 355(o)(4)(E). In all three scenarios, the FDA must fulfill its statutory obligations where it has determined a warning is required. In no circumstance can the FDA determine that an unlabeled safety risk

requires a warning, yet do nothing. To do so would violate the FDA's duty under Section 505(o)(4).

Alternatively, where the FDA has made the considered scientific judgment that no additional labeling is required regarding a potential new safety issue, that ends the inquiry. The FDA has no obligation to continue working with a manufacturer on labeling language where the FDA has concluded that no new labeling language is warranted.

As a consequence of this statutory framework, when the FDA duly considers a potential safety issue and rejects the addition of new safety labeling, that considered rejection provides precisely the clear evidence that supports preemption of state-law claims under *Levine*. While the manufacturer retains ultimate responsibility for the content of the labeling of its medicine, including responsibility for failing to update labeling with new safety information not duly considered by the FDA, the FDA's additional obligations under Section 505(o)(4) require the agency to work with a medicine's sponsor to get the labeling language right if the FDA has determined that a warning should be added. Conversely, if the FDA determines that no new labeling is required, that conclusion by necessity reflects the FDA's assessment that such labeling is not scientifically warranted. Otherwise, the FDA would be in direct violation of its statutory obligations. That decision by the FDA demonstrates, in turn, that the agency would have rejected any effort by the manufacturer to make such a change unilaterally under the CBE provisions — the very inquiry *Levine* instructs the courts to undertake

in determining whether a civil claim would be preempted.

C. The Third Circuit Misapplied the *Wyeth v. Levine* Framework in a Clear-Cut Case of Preemption.

In this case, the FDA considered the new safety information at issue and determined, consistent with its obligations under Section 505(o)(4), that no new safety labeling was warranted. But the FDA did not stop there. It went further by expressly rejecting the sponsor's proposal to add such a warning. As the Solicitor General has pointed out, the Third Circuit's preemption analysis ignores the implication of the FDA's actual rejection of the sponsor's proposed labeling update. *See* U.S. Cert. Br. at 16, 19. Even more fundamentally, the court overlooked the import of the FDA's substantive scientific determination that no new warning was warranted. No rational preemption framework should presume a dereliction of agency duty. But the Third Circuit adopted precisely such a framework in this case. By allowing a jury to attribute the FDA's dispositive rejection to linguistic disagreements, the Third Circuit disregarded the FDA's affirmative obligations under Section 505(o)(4).

Because the Third Circuit did not take proper account of the FDA's affirmative duties, it erroneously concluded that there was insufficient evidence that the FDA would have rejected alternate labeling language regarding atypical femoral fractures. But here there is no dispute that the FDA concluded that

the scientific data on femoral fractures did not support a warning in the labeling, and thus declined to adopt a change to Fosamax's warnings discussing this risk. *See* U.S. Cert. Br. at 16, 19. The FDA's substantive rejection cannot be viewed as simply the FDA's failure to agree with Merck's proposed language. The proposition that the FDA might have accepted a differently-worded warning on atypical femoral fractures assumes that the FDA violated its statutory duties. The FDA considered and rejected the warning at issue without pursuing linguistic negotiations with Merck, thus confirming that the FDA was concerned with the underdeveloped science, not with the language used in the labeling.

If the FDA had determined in 2009 that additional labeling for femoral fractures was needed in the Warnings and Precautions section of the Fosamax label, it would have been obligated *at that time* to work with Merck to determine the contents of that labeling. *See* 21 U.S.C. § 355(o)(4)(C); U.S. Cert. Br. at 22. Indeed, the FDA did exactly that in approving new Adverse Reaction language for Fosamax, which was modified from the proposal that Merck had submitted. Had the FDA determined that an atypical femoral fracture warning was appropriate for the Warnings and Precautions section, it would have similarly initiated similar conversations with Merck to come to an agreement on labeling language.[5]

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[5] In guidance to the industry, the FDA notes, "FDA expects that information that results in changes made only to the ADVERSE

The FDA's subsequent actions further confirm that its rejection of Merck's proposed labeling was not due to a disagreement with Merck's proposed language, but was instead rooted in the FDA's belief that a warning was not appropriate or necessary at that time. After reviewing the evidence Merck submitted in support of its labeling change, the FDA instructed Merck to "hold off" on adding a warning while a task force considered whether any warning was "warranted." Pet. App. 17–18. Only after receiving the task force's recommendation did the FDA conclude that atypical femoral fractures were "'potentially more closely related to'" Fosamax use than it had previously appreciated. Pet. App. 21. At that time, the FDA began working with Merck consistent with its Section 505(o)(4) authority to amend the Fosamax label to include a warning that was backed by adequate science.

The FDA's substantive determination in 2009 that the scientific record did not warrant a labeling change provides the conclusive verification *Lævine* envisions that the FDA would have rejected a request by Merck to make such a labeling change. That the FDA actually rejected Merck's labeling submission

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REACTIONS section, but does not warrant inclusion of other sections (such as WARNINGS AND PRECAUTIONS), would not normally trigger safety labeling changes under section 505(o)(4)." *FDA Guidance for Industry*, *supra*, at 6. This guidance confirms that had the risk of atypical femoral fracture been serious enough to warrant a change in the Warnings and Precautions section, the FDA would have worked with Merck to make those changes using its Section 505(o)(4) authority.

only confirms that result. The Third Circuit's speculation that the FDA might have permitted such a change had Merck asked in some different manner — and its direction that a lay jury should decide the question — cannot be squared with the FDA's statutory obligations. The FDA's rejection of Merck's labeling supplement without initiating labeling discussion provides dispositive confirmation that the FDA did not believe any additional warning was appropriate at that juncture. Because Merck could not have complied with the FDA's federal directives while also including the warning Plaintiffs claim is required under state law, Plaintiffs' claim is preempted.

II. The Court of Appeals Disregarded the Realities of the FDA's Labeling Review, Thereby Threatening Its Effectiveness.

In addition to disregarding the FDAAA's impact on the *Wyeth v. Levine* preemption framework, the Third Circuit also failed to consider the practical implications of its preemption rule. The Third Circuit's standard gives insufficient deference to the policy rationale behind the FDA's extensive labeling authority, particularly following the FDAAA. The Third Circuit's decision also creates conditions under which the FDA's review capabilities could be overwhelmed by labeling submissions, thus hampering its ability to ensure accurate and appropriate labeling. Lastly, the Third Circuit's preemption standard could disincentivize innovation and harm public health.

A. Prescription Medicine Labeling Must Contain the Essential, Scientifically-Grounded Safety Information.

Pharmaceutical labeling strikes a delicate balance. Labeling conveys a wealth of information necessary for the safe and effective use of a medicine. But this information must be communicated in a manner that is useful to healthcare professionals. One way in which labeling achieves this balance is by providing information only when it is scientifically-based.

Striking this balance is critically important because patients may be harmed when labeling communicates unfounded safety information. First, physicians may disregard lengthy labeling if it is weighted down with speculative warnings, causing them to overlook important, scientifically-founded safety information. *See, e.g.*, *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 869 (7th Cir. 2010) ("The resulting information overload [from describing every remote risk] would make label warnings worthless to consumers."); *Thomas v. Hoffman-LaRoche, Inc.*, 949 F.2d 806, 816 n.40 (5th Cir. 1992) (noting that if manufacturers were required to clutter their warnings with "every possible risk," then "physicians [would] begin to ignore or discount the warnings"); Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. at 49,605–06 (unfounded statements in FDA labeling may cause "more important warnings" to be "overshadow[ed]").

Second, warnings that are not grounded in science can discourage the beneficial use of medicines. *See, e.g.*, *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392 (7th Cir. 2010) ("[O]verwarning can deter potentially beneficial uses of the drug by making it seem riskier than warranted . . . ."); *Dowhal v. SmithKline Beecham Consumer Healthcare*, 88 P.3d 1, 14 (Cal. 2004) ("[A] truthful warning of an uncertain or remote danger may mislead the consumer into misjudging the dangers stemming from use of the product, and consequently making a medically unwise decision."); Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. at 49,605–06 ("[O]verwarning . . . may deter appropriate use of medical products . . . ."). All medicines have risks, and all prescribing decisions are based on balancing those risks against potential benefits. Distorting the true nature of that balance, by overstating unfounded or speculative risks, inhibits medical professionals from making optimal prescribing decisions.

The case of bisphosphonates like Fosamax provides a dramatic example of this phenomenon. With an aging U.S. population, the societal risks of decreased bone health are substantial. For instance, looking only at hip fractures, direct medical costs in the first six months after a fracture can be more than $50,000. *See* Jane Brody, *A Perfect Storm for Broken Bones*, N.Y. Times (Feb. 12, 2018), https://www.nytimes.com/2018/02/12/well/bone-fractures-broken-hip-osteoporosis-drugs-treatment-diagnosis.html. With the advent of new medicines like bisphosphonates, Americans experienced a

striking reduction in hip fractures in the 10-year period from 2002 to 2012, but then that reduction suddenly leveled off in 2012. E. Michael Lewiecki et al., *Hip fracture trends in the United States, 2002 to 2015*, 29 Osteoporosis Int'l 717, 717 (2018) ("We found that hip fracture rates declined each year from 2002 to 2012 and then plateaued at levels higher than projected for years 2013, 2014, and 2015."). That leveling off had a real public health impact. *Id.* ("The plateau in age-adjusted hip fracture incidence rate resulted in more than 11,000 additional estimated hip fractures over the time periods 2013, 2014, and 2015."). And this decline in usage can be traced directly to the impact of high-profile litigation and adverse media focusing on the potential rare side effects of bisphosphonates. *See* Gina Kolata, *Fearing Drugs' Rare Side Effects, Millions Take Their Chances with Osteoporosis*, N.Y. Times (June 1, 2016), https://www.nytimes.com/2016/06/02/health/osteoporosis-drugs-bones.html (describing impact of lawsuits and media in dissuading patients from using bisphosphonates); Brody, *supra* ("Currently, many people at risk of a fracture – and often their doctors – are failing to properly weigh the benefits of treating fragile bones against the very rare but widely publicized hazards of bone-preserving drugs, experts say.").

The consequences of getting this critical balance wrong are high, which is exactly why the FDA and manufacturers interact throughout a tightly-regulated process to ensure that labeling appropriately and accurately conveys the risks and benefits associated with all medicines. Through this

process, the FDA brings to bear its expert judgment about whether a risk should appear in a medicine's label and, if so, how best to convey that information without diluting the labeling by including speculative or scientifically-unfounded warnings. The Third Circuit's standard disregards the FDA's expertise by allowing a jury to speculate as to the FDA's reasoning for rejecting labeling. Juries that are not well-versed in the complex duties and responsibilities of the FDA — including its affirmative obligations under the FDAAA — cannot provide the same assurances for consumer safety as the FDA.[6]

B. The Third Circuit's Standard Threatens to Overwhelm the FDA's Review Capabilities.

The Third Circuit's decision also creates perverse incentives that threaten to undermine the FDA's review process. As interpreted by the Third Circuit, "clear evidence" requires a "'smoking gun' rejection letter." Pet. App. 55. That requirement misunderstands the nature of FDA review by assuming that review is limited to the precise verbiage submitted, when in fact, the FDA cannot let linguistic disagreements stand in the way of

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[6] Senator Coburn noted during debate on the FDAAA that, "[o]verwarning, just like underwarning, can similarly have negative effect on public safety and public health.[] In this bill, we have created a clear labeling pathway between the FDA and a drug sponsor in this bill to ensure that consumers get scientifically accurate and appropriate warning of drug safety risks." 153 Cong. Rec. S11840 (daily ed. Sept. 20, 2007) (statement of Sen. Coburn).

medically-warranted warnings. *See* 21 U.S.C. § 355(o)(4)(C). More problematic, the need for a "smoking gun" rejection letter will create an incentive for manufacturers to submit multiple iterations of a warning to maximize the prospect that some future jury will find the FDA's rejection sufficiently clear.

The FDA routinely makes scientific judgments regarding medicine safety. As this case demonstrates, it often makes those judgments without delaying its future work by stopping to issue formal public statements on every judgment that it makes, particularly in those instances where it makes judgments that warnings are not scientifically appropriate. Given that reality, companies facing potentially massive product liability risks will have an incentive to press for definitive rejections of all conceivable labeling variations.

Creating a regime that incentivizes manufactures to inundate the FDA with serial labeling submissions could materially impair the FDA's ability to carry out its mission. In *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), this Court held that state law "fraud-on-the-FDA" claims are preempted, reasoning that such claims incentivize manufacturers "to submit a deluge of information that the [FDA] neither wants nor needs" out of "fear that their disclosures . . . will later be judged insufficient in state court," thereby creating "additional burdens on the FDA[]." *Id.* at 351. The Third Circuit's preemption standard creates the same incentives that *Buckman* found impermissible.

Diverting the attention of the FDA toward litigation-defensive submissions would be an exercise fraught with peril. *See* Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006) ("FDA reviews all [CBE] submissions . . . ."); *Lofton v. McNeil Consumer & Specialty Pharm.*, 672 F.3d 372, 380 (5th Cir. 2012) (when manufacturers are compelled "to flood the FDA with information" to protect against liability, the FDA "loses control over its ability, based on scientific expertise, to prescribe — and intelligently limit — the scope of disclosures necessary for its work"); Br. for the United States as Amicus Curiae Supporting Pet'r at 25, *Wyeth v. Levine*, 555 U.S. 555 (2009) (No. 06-1249) ("[The FDA] could not reasonably be expected to *expressly* reject every possible variant of approved labeling as part of its decisional process. Indeed, it would underestimate the post hoc imagination of lawyers to think such an exhaustion of potential variants by the manufacturer or the agency is even possible."). The Third Circuit's misguided standard, however, would produce such results. As in *Buckman*, the Court should find these incentives impermissible and reverse the Third Circuit's flawed interpretation of *Wyeth v. Levine*.

C. The Third Circuit's Decision Will Discourage Innovation and Harm Public Health.

Bringing a new medicine to market is a lengthy and expensive process. *See Mutual Pharm. Co., Inc. v. Bartlett*, 570 U.S. 472, 476 (2013) ("The process of submitting an NDA is both onerous and lengthy.");

PLIVA, Inc. v. Mensing, 564 U.S. 604, 612 (2011) (citations omitted) ("[A] manufacturer seeking federal approval to market a new drug must prove that it is safe and effective and that the proposed label is accurate and adequate. . . . Meeting those requirements involves costly and lengthy clinical testing."). Before studying a new medicine in humans, a pharmaceutical company must conduct a broad range of laboratory and animal studies to test how the medicine works and assess its safety. 21 C.F.R. § 312.23(a)(8). If the results are promising, the company submits an Investigational New Drug application ("IND") to the FDA, outlining the preclinical study results and offering a plan for clinical trials in humans. 21 U.S.C. § 355(i)(2); 21 C.F.R. § 312.20(a)–(b). Only after an IND is submitted to the FDA and goes into effect can a company begin to study the prospective medicine in humans.

Human clinical trials generally occur in three phases, each of which typically must be completed before the potential new medicine may undergo FDA review and approval. 21 C.F.R. § 312.21. On average, the clinical trial phase takes six to seven years. PhRMA, *Modernizing Drug Discovery, Development and Approval* 1 (2016), http://phrma-docs.phrma.org/sites/default/files/pdf/proactive-policy-drug-discovery.pdf.

Following the satisfactory completion of clinical trials, a company can seek the FDA's approval to market the medicine by submitting a New Drug Application ("NDA"). 21 U.S.C. § 355(b)(1). The NDA,

which must contain, among other things, the results of the clinical and pre-clinical testing, proposals for manufacturing, and proposed labeling for the new medicine, *id.*, often exceeds 100,000 pages in length, PhRMA, *Biopharmaceutical Research & Development: The Process Behind New Medicines* 14 (2015), http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf.

This process is tremendously expensive. On average, developing and obtaining FDA approval of a new medicine takes ten to fifteen years and costs $2.6 billion. *Biopharmaceuticals in Perspective*, *supra*, at 29; *see also* Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20 (2016).[7] PhRMA's member companies invest approximately one quarter of their total annual domestic sales on research and development — an estimated $65.5 billion in 2016. *Biopharmaceuticals in Perspective*, *supra*, at 35. The

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[7] These estimates actually understate the cost of approval, as the FDA frequently requires that a sponsor undertake additional clinical studies after approval. *See* 21 U.S.C. § 355(o)(3)(A). According to one estimate, more than three quarters of all new medicine approvals are accompanied by a commitment from the sponsor to conduct one or more post-marketing, or "Phase IV," studies. Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 Food & Drug L.J. 295, 300 (2006). PhRMA's member companies spent more than $7.4 billion in 2016 conducting these studies. PhRMA, *Annual Membership Survey* 6 tbl.4 (2017), http://phrma-docs.phrma.org/files/dmfile/PhRMA_membership-survey_2017.pdf.

biopharmaceutical industry as a whole invested $75.3 billion in research and development in 2015. *Id.* at 31.

These research efforts also involve tremendous risk, as most compounds invented never attain FDA approval. Only one out of every 5,000 to 10,000 compounds under development, and less than 12 percent of medicines entering clinical trials, obtains FDA approval. Press Release, PhRMA, PhRMA Statement Regarding Benefits of New Medicines (Apr. 30, 2013), https://www.phrma.org/press-release/phrma-statement-regarding-benefits-of-new-medicines; *Biopharmaceuticals in Perspective*, *supra*, at 29; *see also, e.g.*, Jared S. Hopkins & Michelle Cortez, *Lilly's Alzheimer's Disease Drug Fails in Final-Stage Trial*, Bloomberg (Nov. 23, 2016, 6:52 AM), https://www.bloomberg.com/news/articles/2016-11-23/lilly-s-alzheimer-s-disease-drug-fails-in-final-stage-trial (discussing an innovator's $3 billion investment in an Alzheimer's treatment medication that failed at the final stage of clinical testing).

Given the enormous costs associated with researching and developing new medicines, the scope of litigation risk has a significant effect on a company's decision to invest in innovation. *See* W. Kip Viscusi et al., *A Statistical Profile of Pharmaceutical Industry Liability, 1976-1989*, 24 Seton Hall L. Rev. 1418, 1419 (1994) ("[T]he net effect of the surge in liability costs ha[s] been to discourage innovation in the pharmaceutical industry . . . ."); Richard A. Epstein, *Legal Liability for Medical Innovation*, 8 Cardozo L. Rev. 1139, 1153 (1987) ("If in the aggregate the net gains are wiped out by the liability costs, then

the product will no longer be made."). The scope of litigation against pharmaceutical companies is already immense and rapidly expanding. Last year, 21,335 product liability lawsuits were filed against pharmaceutical companies in federal courts alone, up from 6,791 lawsuits in 2012 and just 2,700 lawsuits in 2001.[8] Today, out of sixty-nine pending product liability multidistrict litigation proceedings, twenty-eight involve pharmaceuticals.[9] By comparison, between 1960 and 1999, there were only five MDL product liability actions involving FDA-approved medicines.[10]

The anti-nausea drug Bendectin, used to treat severe morning sickness in pregnant women, illustrates how unpredictable and unfounded litigation risks influence a company's decision to invest in innovation. After Bendectin was alleged to be the cause of birth defects in thousands of lawsuits, its manufacturer withdrew the medicine from the

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[8] *See* Admin. Office of the U.S. Courts, Table C-2A: *U.S. District Courts — Civil Cases Commenced, by Nature of Suit, During the 12-Month Periods Ending September 30, 2012 Through 2017*, http://www.uscourts.gov/sites/default/files/data_tables/jb_c2a_0930.2016.pdf; Lisa Girion, *State Vioxx Trial Is Set as Drug Suits Boom*, L.A. Times, June 27, 2006, at C1.

[9] *See* U.S. Judicial Panel on Multidistrict Litig., MDL Statistics Report — Docket Type Summary (Sept. 17, 2018), http://www.jpml.uscourts.gov/sites/jpml/files/Pending_MDL_Dockets_By_Type-September-17-2018.pdf.

[10] *See* Deborah R. Hensler, *Has the Fat Lady Sung? The Future of Mass Toxic Torts*, 26 Rev. Litig. 883, 897–902 tbl.1 (2007).

market in 1983. Only later was it vindicated by scientific studies showing that Bendectin posed no maternal fetal risk.[11] In 2013, after nearly thirty years off the market, Bendectin returned under a new name.[12] In the interim, hospital admissions for excessive vomiting during pregnancy had doubled, costing the U.S. economy $1.7 billion annually in time lost from work, caregiver time, and hospital expenses apart from the avoidable human suffering.[13]

The development of medicines for high-risk and vulnerable populations is especially subject to this phenomenon. By 1990, for example, eight of the nine major U.S. pharmaceutical companies that had been involved in researching and developing new

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[11] *See* Joseph Sanders, *From Science to Evidence: The Testimony on Causation in the Bendectin Cases*, 46 Stan. L. Rev. 1, 7 (1993); Robert Brent, *Medical, Social, and Legal Implications of Treating Nausea and Vomiting of Pregnancy*, 186 Am. J. Obstetrics & Gynecology S262, S262–63 (2002); *see also* David E. Bernstein, *The Breast Implant Fiasco*, 87 Calif. L. Rev. 457, 460 (1999); Lars Noah, *Triage in the Nation's Medicine Cabinet: The Puzzling Scarcity of Vaccines and Other Drugs*, 54 S.C. L. Rev. 371, 392 (2002).

[12] *See* News Release, FDA, *FDA Approves Diclegis for Pregnant Women Experiencing Nausea and Vomiting* (Apr. 8, 2013).

[13] *See* Nina Nuangchamnong & Jennifer Niebyl, *Doxylamine Succinate–Pyridoxine Hydrochloride (Diclegis) for the Management of Nausea and Vomiting in Pregnancy: An Overview*, 6 Int'l J. Women's Health 401, 401–02 (2014).

contraceptives had abandoned their efforts.[14] According to a contemporaneous report from the National Research Council and the Institute of Medicine, "recent products liability litigation and the impact of that litigation on the cost and availability of liability insurance have contributed significantly to the climate of disincentives for the development of contraceptive products." *Id.* at 141. In 1989, the inventor of the birth control pill, Carl Djerassi, recommended changes to the product liability regime, commenting that "[t]he United States is the only country other than Iran in which the birth-control clock has been set backward during the past decade."[15] The executive director of the Society for the Advancement of Women's Health Research similarly testified before Congress that "the current liability climate is preventing women from receiving the full benefits that science and medicine can provide." S. Rep. No. 104-69, at 7 (1995).

In *Levine*, the Court accepted the argument that diminished incentives for research and production of medicines might be offset by the possibility of uncovering "unknown drug hazards" and "incentives for drug manufacturers to disclose safety risks

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[14] Nat'l Research Council, Comm. on Contraceptive Dev., & Inst. of Med., Div. of Int'l Health, *Developing New Contraceptives: Obstacles and Opportunities* 59 (Luidi Mastroianni et al. eds., 1990), https://www.nap.edu/read/1450.

[15] Carl Djerassi, *The Future of Birth Control*, Wash. Post (Sept. 10, 1989), https://www.washingtonpost.com/archive/opinions/1989/09/10/the-future-of-birth-control/7e25f2cc-ae35-4a79-8daf-031db02f81be/?utm_term=.c627032fecdb.

promptly." 555 U.S. at 579. But where the FDA has identified a potential safety risk and rejected the need for a warning, or where a manufacturer brings proposed labeling for a safety risk to the FDA and the agency disagrees about the necessity of a warning, subsequent civil litigation is unlikely to have offsetting health benefits. *See Levine*, 555 U.S. at 582 ("But it is also possible that state tort law will sometimes interfere with the FDA's desire to create a drug label containing a specific set of cautions and instructions.") (Breyer, J., concurring); *see also Riegel v. Medtronic, Inc.*, 552 U.S. 312, 325 (2008) (whereas "the experts at the FDA" apply a "cost-benefit analysis," a jury "sees only the cost of a more dangerous design, and is not concerned with its benefits; the patients who reaped those benefits are not represented in court"); 150 Cong. Rec. S8657 (daily ed. July 22, 2004) (statement of former FDA Chief Counsels) ("If every state judge and jury could fashion their own labeling requirements for drugs and medical devices, . . . FDA's ability to advance the public health by allocating scarce space in product labeling to the most important information would be seriously eroded."). By discounting the rigorous FDA-supervised process manufacturers undertake to bring a medicine to market and encouraging civil litigation, the Third Circuit's decision hampers innovation and harms public health.

CONCLUSION

The judgment of the court of appeals should be reversed.

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In The Supreme Court of the United States

MERCK SHARP & DOHME CORP.,

Petitioner,

v.

DORIS ALBRECHT, ET AL.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Third Circuit

BRIEF OF THE PRODUCT LIABILITY ADVISORY COUNCIL, INC. AND THE CHAMBER OF COMMERCE OF THE UNITED STATES OF AMERICA AS *AMICI CURIAE* IN SUPPORT OF PETITIONER

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BRIEF OF THE PRODUCT LIABILITY ADVISORY COUNCIL, INC. AND THE CHAMBER OF COMMERCE OF THE UNITED STATES OF AMERICA AS *AMICI CURIAE* IN SUPPORT OF PETITIONER

INTEREST OF THE *AMICI CURIAE*[1]

The Product Liability Advisory Council, Inc. (PLAC) is a non-profit professional association of corporate members representing a broad cross-section of American and international product manufacturers. Its 84 corporate members make and sell a wide variety of products, including automobiles, trucks, aircraft, electronics, cigarettes, tires, chemicals, pharmaceuticals, and medical devices.[2] PLAC's primary purpose is to file *amicus curiae* briefs in cases that raise issues affecting the development of product liability litigation and have potential impact on PLAC's members.

The Chamber of Commerce of the United States of America (Chamber) is the world's largest business federation. It represents 300,000 direct members and indirectly represents the interests of more than three

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[1] All parties have filed blanket letters of consent with the Clerk. Pursuant to S. Ct. Rule 37.6, *amici* state that no counsel for a party wrote this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity, other than the *amici curiae*, their members, or their counsel, has made a monetary contribution to this brief's preparation or submission.

[2] For a full list of PLAC's corporate members, see https://plac.com/PLAC/AboutPLACAmicus.

million companies and professional organizations of every size, in every industry sector, from every region of the country. An important function of the Chamber is to represent the interests of its members in matters before Congress, the Executive Branch, and the courts. To that end, the Chamber regularly files *amicus* briefs in cases that raise issues of vital concern to the Nation's business community.

This is such a case. It presents an important question that has produced uncertainty and serious confusion in the lower courts involving the scope of implied conflict preemption in the aftermath of this Court's decision in *Wyeth* v. *Levine*, 555 U.S. 555 (2009). PLAC, the Chamber, and their members have a vital interest in the proper resolution of the question presented.

STATEMENT

1. *The Supremacy Clause and Implied Conflict Preemption.* Congress has the authority to specify the extent to which federal statutes preempt state and local law, and the United States Code contains many such "express" preemption provisions. Even in the absence of such specification, however, state and local laws that conflict with federal law are preempted "by direct operation of the Supremacy Clause." *Brown* v. *Hotel & Restaurant Employees & Bartenders Int'l Union Local 54*, 468 U.S. 491, 501 (1984). Although this Court has referred to "impossibility," "obstacle" and ordinary "conflict" preemption as forms of implied preemption, these "terminological" distinctions cannot obscure the fundamental principle that the Supremacy Clause reaches *all* cases where there is an *actual* or *direct* conflict between state and federal

requirements. *Geier* v. *Am. Honda Motor Co.*, 529 U.S. 861, 873-74 (2000); see also *Hines* v. *Davidowitz*, 312 U.S. 52, 67 (1941).

The Supremacy Clause serves a vital structural role in our Nation's government by protecting federal laws and programs against interference by subordinate governments. Like express preemption clauses, the Supremacy Clause also helps to create unified markets for nationally distributed goods and services by ensuring that uniform federal regulation – often the product of expert agency decision-making under authority delegated by Congress – is not undermined by state or local law, including state tort law as applied by lay juries. And the Supremacy Clause ensures that regulated individuals, businesses, and other entities are not placed in the impossible position of being compelled to obey directly conflicting obligations imposed by federal and state law. This case raises an important question concerning the Supremacy Clause's meaning in the context of prescription pharmaceuticals.

2. *Wyeth* v. *Levine*. In *Levine*, this Court addressed the preemptive effect of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, implementing regulations relating to drug labeling, and FDA regulatory oversight on state-law failure-to-warn claims against prescription-drug manufacturers. See Pet. Br. 2-6 (describing regulatory framework). Federal law, this Court explained, does not preempt such claims if applicable regulations would have allowed the manufacturer unilaterally to alter its previously approved labeling and FDA ultimately would have approved that change, but does preempt if FDA would have rejected

the change. 555 U.S. at 568, 570-71 (discussing "Changes Being Effected" (CBE) regulation), 21 C.F.R. § 314.70(c)). In *Levine*, the manufacturer had asserted both that FDA "intended to prohibit it from strengthening the warning" when the agency originally approved the drug and that FDA would have rejected the warning change proposed by plaintiff, but the Vermont courts rejected those contentions. This Court affirmed the Vermont Supreme Court's resulting no-preemption ruling, observing that the record lacked "clear evidence" supporting the manufacturer's contentions. *Id.* at 571-72 & nn.5-6. In fact, this Court explained, the record contained "*no* evidence * * * that either the FDA or the manufacturer gave more than passing attention to" the risks in question. *Id.* at 572 (internal quotation marks omitted; emphasis added).

3. *The Decisions Below.* This case arises out of a multi-district litigation (MDL) involving more than a thousand state-law tort actions, including claims for failure to warn, brought against petitioner Merck Sharpe & Dohme Corp. (Merck), which manufactures the osteoporosis drug Fosamax. Among other things, plaintiffs claimed Merck should have provided a stronger warning concerning the risk of certain bone fractures.

Following a bellwether trial – and based on a painstaking analysis of "a complete record" (including extensive documentary and other evidence regarding FDA's oversight of the drug's labeling) – the district court concluded that "preemption is warranted because there is clear evidence that the FDA would not have approved a change to the Precautions section

of the Fosamax label prior to" plaintiff's injury. Pet. App. 164a, 168a, 169a-174a; see also *id.* at 156a-162a.

The Third Circuit vacated and remanded. Pet. App. 1a-95a. Parting company with other courts, it held that *Levine*'s unelaborated reference to "clear evidence" was meant to impose on defendant a heightened standard of proof akin to "clear and convincing evidence" under which defendant must prove that FDA would have rejected the proposed warning change. Breaking additional new ground, the court ruled that whether FDA would have rejected a warning is a question *for the jury*, even where, as here, the historical facts are undisputed. Under that approach, a manufacturer cannot prevail pre-trial, as a matter of law, unless there is a "smoking gun" FDA rejection letter from which a jury could only find the claim preempted. Pet. App. 36a-37a, 54a-55a. Based on those demanding standards, the Third Circuit opined that a reasonable jury "*could* conclude" that FDA would have allowed the labeling change sought by plaintiffs (even though FDA had in fact *rejected* proposed warning language concerning the very risk in question). *Id.* at 67a. The court remanded for juries in individual cases to decide, following a full trial, what FDA would have done.

INTRODUCTION AND SUMMARY OF ARGUMENT

This case raises an important question of federal law – and the meaning of the Supremacy Clause – that has vexed the lower courts and is of paramount importance to the pharmaceutical industry. The central question turns on the meaning of certain language in *Wyeth* v. *Levine*, 555 U.S. 555 (2009) –

specifically, this Court's statement that an "impossibility" preemption defense was not available on the particular record developed there because there was not "clear evidence" that FDA would have rejected the warning sought by plaintiff. *Id.* at 571. In the decision below, the Third Circuit adopted a novel gloss on those two words in *Levine* and, in so doing, erected an exceedingly high – and unwarranted – barrier to pharmaceutical manufacturers' conflict preemption defenses.

I. The Third Circuit held that this Court's unelaborated reference to "clear evidence" was intended to impose on defendants the "clear and convincing" burden of proof. That is mistaken. Contrary to the Third Circuit's view, *Levine* did not adopt a heightened burden of proof for prescription pharmaceutical cases. Instead, this Court's reference to "clear evidence" merely reflects well-settled precedent establishing that conflict preemption requires demonstration of an *actual*, rather than merely a *hypothetical or potential*, conflict between federal and state law. So much is apparent from the authorities cited by this Court in *Levine*. See, *e.g.*, *Geier* v. *Am. Honda Motor Co.*, 529 U.S. 861, 884-85 (2000) (conflict preemption "turns on the identification of [an] 'actual conflict[]'" and should not be found "too readily in the absence of *clear evidence* of a *conflict*") (emphasis added); *English* v. *General Electric Co.*, 496 U.S. 72, 90 (1990) (rejecting conflict preemption argument where conflict was "too speculative"). Indeed, *Geier* specifically *rejected* as unworkable and unwieldy a proposal to impose on defendants a "special burden" to establish conflict preemption. It is implausible, to say the least, that this Court created exactly such a special burden in

Levine while citing and relying on *Geier*. Moreover, the parties neither briefed nor argued the burden-of-proof issue, which was unnecessary to decide anyway since there was *no* evidence FDA would have rejected the relevant warning.

In adopting the demanding "clear and convincing" standard of proof, the Third Circuit not only overlooked the origins of the "clear evidence" language in this Court's prior preemption cases but also relied on various *non-preemption* decisions that (as petitioner amply demonstrates) are all readily distinguishable. See Pet. Br. 45-46. The cited cases involve either instances where Congress has specified a higher standard or such standard is needed to protect a compelling interest, which is not true here. Notably, the Third Circuit also ignored the procedural posture of *Levine*, in which this Court could not have rejected any *factual* determinations of two state courts absent "extraordinary" circumstances, *i.e.*, "clear evidence" those determinations were erroneous.

As petitioner and the Solicitor General both explain, this Court could elect to reverse the Third Circuit's decision without addressing the meaning of "clear evidence" in *Levine*, simply by distinguishing that case (as not involving an FDA decision rejecting the proposed warning in question). But PLAC and the Chamber urge the Court not to rule so narrowly. Instead, this Court should treat the meaning of "clear evidence" in *Levine* as a threshold issue and clarify it. Doing so would go far toward dispelling the serious confusion – and conflicting results and approaches – that have plagued the lower-court decisions since *Levine*. And only this Court can clarify what it meant by "clear evidence."

More specifically, PLAC and the Chamber urge this Court to clarify that "clear evidence" means nothing more than it does in other conflict preemption cases: evidence of an actual, as opposed to a merely hypothetical, conflict between state and federal law. Nothing in *Levine* – where this Court, like both Vermont courts, resolved the preemption issue *as a matter of law* – was intended to adopt a standard of proof *for facts*, much less one different from the ordinary preponderance-of-the-evidence standard. Finally, this Court should leave to the lower courts the exploration, in the first instance, of additional arguments about how any burden of proof might be structured.

II. The Third Circuit also erred in concluding that the question whether FDA would have rejected a proposed warning is a *fact* question *for the jury*, even when (as in this case) the historical facts are undisputed. As petitioner and the Solicitor General demonstrate, it was wrong to apply that approach in this case which, unlike *Levine*, involved an *actual* decision by FDA to reject a warning concerning the risk that was at the center of respondents' claim. The meaning and effect of FDA's decision presents a *legal* question for the court, not a factual question for a jury.

Although this rationale would suffice to reverse the decision below, PLAC and the Chamber urge the Court to go further and make clear that in all cases involving prescription drug manufacturers, issues relating to conflict preemption – including counterfactual questions concerning whether FDA would have rejected a warning the manufacturer never proposed – are properly resolved by courts, not juries. The Third Circuit was wrong to believe that

the proper decisionmaker for such counterfactual issues was left open in *Levine*; in fact, both Vermont courts and this Court decided that issue for themselves without suggesting it was properly for a jury. That approach, which as the Third Circuit acknowledged has since been followed by many lower courts, fits comfortably within the traditional framework for resolving conflict preemption issues. It is also consistent with the history and form of the Supremacy Clause – the basis for conflict preemption – which expressly refers to "Judges" and is cast in the form of a *non obstante* clause specifically directed at judicial interpretation.

The Third Circuit believed it could tease out from the legal conflict preemption analysis the specific question of what the FDA would have done under counterfactual circumstances, because that question purportedly is one of fact, not law. But whether that issue is properly characterized as one of fact (unlikely) or law, or mixed law and fact, it plainly requires the decisionmaker to understand the complex backdrop of FDA's regulations and procedures, including the standards the agency applies to determine whether there is a sufficient scientific basis to provide additional warnings (or other cautionary statements) in various parts of the highly regulated drug labeling. It may also, as here, require the decisionmaker to understand how the agency deals with concerns regarding the appropriate wording of proposed labeling changes. See U.S. Inv. Br. 5-6, 19-22. In addition, the decisionmaker, again as here, may have to interpret FDA decisions and communications, which are properly "read in the context of [the manufacturer's] underlying labeling supplement and the surrounding regulatory framework and related

FDA actions." *Id.* at 15. As the government correctly notes, "[e]ven if disputed subsidiary factual questions were relevant to determining the meaning and effect of the agency's 2009 decision, the ultimate inquiry would remain a legal one." *Ibid.*

Finally, in other settings that call for predictive determinations about what other institutional actors *would have done* under circumstances that did not actually occur, courts have themselves often resolved the issue as a matter of law. Examples include harmless error analysis, which asks what the outcome of a court proceeding would have been if error had not occurred, and severability analysis, which asks whether Congress would have enacted the same statute if it had known that one or more portions would later be invalidated; see *Murphy* v. *National Collegiate Athletic Ass'n*, 138 S. Ct. 1461, 1482 (2018). Accordingly, there is nothing unusual about courts rather than juries deciding counterfactual issues in the context of conflict preemption issues under *Levine*. And, of course, that approach would avoid the practical problems that flow from treating the counterfactual issues as factual questions for lay juries.

III. The Third Circuit should also be reversed – and its problematic reasoning expressly disapproved – because it ignored this Court's decisions establishing that conflict preemption may not be impaired or evaded altogether through tactics such as artful pleading by plaintiffs, *Aetna Health Inc.* v. *Davila*, 542 U.S. 200, 214 (2004), or resort to mere speculative possibilities, *PLIVA, Inc.* v. *Mensing*, 564 U.S. 604, 623 (2011), or overbroad arguments that could be used to defeat preemption in essentially all

cases, *Mutual Pharmaceutical Co.* v. *Bartlett*, 570 U.S. 472, 514-15 (2013).

Unless corrected, the Third Circuit's decisions to (a) adopt the clear-and-convincing standard of proof, and (b) assign to juries, rather than courts, the authority to make decisions about what FDA would have done under counterfactual circumstances, will have predictably negative effects. Those rulings will deprive litigants of the recognized benefits of preemption as a dispositive issue that can be resolved before trial; create perverse incentives for manufacturers to burden FDA with constant proposed labeling changes for preemption purposes (an institutional burden this Court declared to be important in *Buckman Co.* v. *Plaintiffs' Legal Committee*, 531 U.S. 341 (2001)); and inhibit drug development by imposing massive additional litigation costs on drug manufacturers in the rising tide of product liability litigation against them. Unless corrected by this Court, the Third Circuit's flawed reasoning will also encourage litigants in other preemption settings both to argue for heightened burdens of proof and to attempt to shift the responsibility for policing violations of the Supremacy Clause to lay juries.

ARGUMENT

I. THIS COURT SHOULD CLARIFY *LEVINE*'S REFERENCE TO "CLEAR EVIDENCE," WHICH THE THIRD CIRCUIT MISINTERPRETED

As both petitioner and the Solicitor General demonstrate, this Court could reverse the Third

Circuit's flawed decision without addressing or clarifying the meaning of *Levine*'s ambiguous reference to "clear evidence." It could do so on the ground that this case, unlike *Levine*, turns on the meaning and effect of an *actual* FDA decision regarding a labeling supplement, not a purely hypothetical scenario. As both petitioner and the Solicitor General show, the Third Circuit failed to recognize that, in this setting, the conflict preemption issue raises a question of law for the court, not the jury – and that issue should have been resolved in favor of petitioner because FDA rejected the warning plaintiffs said should have been provided. Such a narrow resolution of this case, however, would leave unaddressed the lower courts' considerable confusion concerning what this Court meant in *Levine*. For that reason, and because only this Court can clarify what it meant in *Levine*, PLAC and the Chamber urge the Court to address and clarify *Levine*'s reference to "clear evidence." Doing so would both prevent the Third Circuit's flawed interpretation from creating any further mischief and bring greater uniformity to this important area of federal law.

A. There Is Serious Confusion In The Lower Courts Over The Meaning Of *Levine*

As the Third Circuit recognized (Pet. App. 33a-36a), there is rampant confusion in the lower courts over the meaning of *Levine*'s reference to "clear evidence." The court of appeals correctly noted that the meaning of this language, on its face, was "cryptic" and "lower courts have struggled to make it readily administrable." Pet. App. 28a. The Third Circuit also acknowledged that at least two different approaches

have been developed in the lower courts, one "more complex" than the other – and then proceeded to reject both in favor of yet a third reading. *Id.* at 33a-35a.

The confusion over the meaning of "clear evidence" extends well beyond that recognized by the Third Circuit. On the same record involving the same warning for Children's Motrin, the Seventh Circuit and Massachusetts Supreme Judicial Court (SJC) reached diametrically opposed conclusions regarding conflict preemption. Compare *Robinson* v. *McNeil Consumer Healthcare*, 615 F.3d 861, 869-70, 873 (7th Cir. 2010) (concluding there was "clear evidence" FDA would have rejected proposed warning change) with *Reckis* v. *Johnson & Johnson*, 28 N.E.3d 445, 457-60 (Mass. 2015) (reaching opposite conclusion). Such conflicting outcomes necessarily reflect divergent understandings of what is required by *Levine*.

Further, there are multiple tertiary disagreements – and much confusion – in the lower courts over precisely what qualifies as "clear evidence." Compare, *e.g.*, *Aaron* v. *Wyeth*, 2010 WL 653984, at *6 (W.D. Pa. Feb 19, 2010) (holding manufacturer's proposal to FDA to add warning and agency's rejection not "clear evidence" because manufacturer "did not press its position" but "acquiesced" in FDA decision) with *Dobbs* v. *Wyeth Pharmaceuticals*, 797 F. Supp. 2d 1264, 1279 (W.D. Okla. 2011) ("This court disagrees with *Aaron*'s interpretation of the proof standard announced in *Levine*."). In their *amicus* brief at the petition stage (at 10-12), PLAC and the Chamber documented this widespread confusion in the lower-court decisions. Commentators have also acknowledged it. See Thomas Ayala & Elizabeth Graham, *Overcome the*

Clear Evidence Defense, 52 Trial 32, 34 & nn. 13-16 (July 2016) (acknowledging split of authority and discussing additional cases); Michael Gallagher, *Clear Evidence of Impossibility Preemption After Wyeth v. Levine*, 51 GONZ. L. REV. 439, 440-42 (2015-2016) ("[c]ourts have issued divergent opinions").[3]

This Court should decide this case in a way that eliminates this confusion. The need for clarification is underscored by the large and growing body of federal product-liability litigation in which the issue typically arises.[4] The Court has discretion to resolve this case in any way it sees fit, and it would be perfectly sensible to address the meaning of *Levine*'s reference to "clear evidence" as a threshold legal issue (as, indeed, the Third Circuit did, see Pet. App. 28a-29a, 33a-37a). As next explained, the Third Circuit adopted an interpretation of *Levine* that was fundamentally flawed and in need of correction.

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[3] The misunderstanding of how the conflict preemption inquiry should be conducted is also reflected in the suggestion of various lower courts that preemption cannot be established unless a manufacturer *actually proposes* the allegedly missing warning, the FDA *actually rejects the manufacturer's proposal*, or both. Requiring such proof denies preemption in precisely those cases involving the most scientifically unfounded warnings, which *no* manufacturer would ever propose (and FDA *unquestionably* would reject). That cannot possibly be the law, nor can it be what this Court meant in *Levine*.

[4] The MDL proceedings in this case alone involve more than 1000 lawsuits. As PLAC and the Chamber showed in the petition-stage brief (at 23-24), in recent years there has been a sharp rise in the number of federal product liability lawsuits (and MDLs) against pharmaceutical manufacturers.

B. The Third Circuit Misunderstood *Levine*'s Reference To "Clear Evidence"

The Third Circuit concluded that this Court's unelaborated reference to "clear evidence" was intended to impose a special, heightened burden of proof – to require, in other words, more than the usual mere preponderance of the evidence.[5] Relying on that reading, the Third Circuit expressly adopted the "clear and convincing" standard, whereas other lower courts have used different formulations that may be more or less demanding. Pet. App. 35a, 37a. See, *e.g.*, *Mason* v. *Smithkline Beecham Corp.*, 596 F.3d 387, 391 (7th Cir. 2010) (describing "clear evidence" as an "exacting" and "stringent" standard); *Forst* v. *SmithKline Beecham Corp.*, 639 F. Supp. 2d 948, 953 (E.D. Wis. 2009) (under *Levine* "a defendant drug manufacturer faces an exacting burden"). In concluding that by "clear evidence" this Court really meant "clear *and convincing*" proof, the Third Circuit also relied on various non-preemption decisions of this Court that, as petitioner demonstrates, are all readily distinguishable because they involve either instances where Congress has specified a higher standard or

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[5] As petitioner demonstrates (Br. 43-44), standards of proof apply to issues of *fact*; evidentiary standards such as "clear and convincing proof" do not apply to questions of law. See *Microsoft Corp.* v. *i4i Ltd. Partnership*, 564 U.S. 91, 100 n.4 (2011); *id.* at 114 (Breyer, J., concurring). As explained below, conflict preemption issues under *Levine* should be resolved by courts, rather than juries, not only in cases (such as this) where the issue turns on ascertaining the meaning and effect of an FDA labeling decision based on undisputed historical facts, but also in cases where there are disputes over what the FDA might have done in counterfactual circumstances.

such standard is needed to protect a compelling interest. See Pet. Br. 45-46; Pet. App. 36a-37. Here, in contrast, the important interest at stake is that underlying the Supremacy Clause – and it cuts *against* the higher burden invented by the Third Circuit.

The Third Circuit misread *Levine*. For starters, it is highly implausible to assume this Court adopted a heightened burden of proof without any briefing or mention by the parties of the burden-of-proof issue. That is all the more unlikely because in *Levine* the manufacturer had provided *no* evidence FDA would have rejected the relevant labeling change – so there was simply no need to the reach the question whether anything more than a preponderance of the evidence was required. See 555 U.S. at 572 (manufacturer "does not argue that it attempted to give the kind of warning required by the Vermont jury"); *ibid.* ("trial court found *no evidence* in this record that either the FDA or the manufacturer gave more than passing attention to the issue of IV-push versus IV-drip administration") (internal quotation marks omitted; emphasis added). The Third Circuit's interpretation ignores or disregards this context.

Nor is this the only way in which the Third Circuit ignored aspects of *Levine* that bear on the meaning of "clear evidence." In *Levine*, this Court was evaluating the drug manufacturer's preemption arguments in light of *factual findings on historical facts* made *by two lower state courts* concerning (1) whether other warnings the manufacturer proposed and FDA rejected were materially different from the allegedly defective warning that actually accompanied the product, and (2) whether FDA

intended to prohibit the manufacturer from strengthening its warning. See 555 U.S. at 572 & n.5. This Court's statement that there must be "clear evidence" was no doubt informed by this procedural posture and what would have been necessary to overcome the state courts' findings. See *324 Liquor Corp.* v. *Duffy*, 479 U.S. 335, 351 (1987) (this Court "customarily accept[s] the factual findings of state courts in the absence of exceptional circumstances"); see also David Geiger & Andrew London, *Wyeth's "Clear Evidence" Language: Clearly Misunderstood*, Law360 (Jan. 12, 2016) ("'clear evidence' language was necessitated by the fact that the preemption issue turned on factual findings made by the Vermont courts, which the Supreme Court could not ordinarily reverse absent exceptional circumstances"). The Third Circuit's reading of *Levine* ignores the case's procedural posture.

But the Third Circuit's interpretation is flawed for a more fundamental reason: it utterly fails to take account of the backdrop of this Court's own *conflict preemption* decisions, which repeatedly have alluded to the need for "clear evidence" to establish conflict preemption and on which this Court relied in *Levine*. Had the Third Circuit done so, it would have recognized that, far from announcing a heightened standard of proof, *Levine*'s reference to "clear evidence" merely reflects well-settled and longstanding principles governing conflict preemption.

Federal preemption is usually raised as an affirmative defense. And in civil actions, the ordinary standard of proof on issues of fact is by a

preponderance of the evidence.[6] Thus, a defendant ordinarily must prove any facts necessary for a preemption defense by a preponderance of the evidence.[7] In a long line of cases, this Court has made clear that ordinarily the proponent of conflict preemption must demonstrate an *actual* conflict

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[6] See also note 5, *supra*. Although preemption is a *legal* defense, sometimes (as in this setting) the defense can hinge on case-specific regulatory facts and circumstances. In every conflict preemption case, however, a *court* (1) ascertains the meaning of state law; (2) determines the meaning of federal law; and (3) makes a legal judgment whether the former conflicts with, or serves as an obstacle to, the latter. *Perez* v. *Campbell*, 402 U.S. 637, 644 (1971).

[7] Courts and commentators have suggested that, in prescription-drug failure-to-warn cases, the burden of proof ought to be structured differently and placed on plaintiff in whole or at least in part. See Geiger & London, *supra*, Law360 (arguing that, in light of federal regulatory scheme, plaintiff should bear burden to prove what constitutes an *exception* to the preemption that would otherwise exist once defendant proved it was using FDA-approved labeling); *Utts* v. *Bristol-Myers Squibb Co.*, 2017 WL 1906875, at *9, *19 (S.D.N.Y. May 8, 2007) (only after plaintiff "prove[s] the existence of newly acquired information" allowing a manufacturer to submit a CBE does burden shift to manufacturer to show that FDA would have rejected labeling change). And this Court has made clear that preemption is not always "in the nature of an affirmative defense." *Int'l Longshoremen's Ass'n* v. *Davis*, 476 U.S. 380, 381-82, 387-89 (1986) (involving so-called "*Garmon*" preemption under the National Labor Relations Act). Moreover, in cases (unlike this one) where the manufacturer has not proposed any warning because there is *no scientific basis* for the asserted risk, it might well make sense to place the initial burden on plaintiff to demonstrate that the claimed risk is real before requiring the manufacturer to show FDA would nevertheless have rejected the warning. This Court should resolve this case in a way that does not foreclose litigants from making arguments along these lines in the lower courts.

between state and federal law – potential or hypothetical conflicts are not enough. The preemptive conflict, in other words, must be "clear." See, *e.g.*, *Geier* v. *Am. Honda Motor Co.*, 529 U.S. 861, 884 (2000) (conflict preemption "turns on the identification of 'actual conflict[]'"); *English* v. *General Electric Co.*, 496 U.S. 72, 90 (1990) (rejecting conflict preemption where claimed conflict was "too speculative"); *Rice* v. *Norman Williams Co.*, 458 U.S. 654, 664 (1982) (Court's decisions "enjoin seeking out conflicts between state and federal regulation where none *clearly* exists") (emphasis added; internal quotation marks omitted). "Clear evidence" in this setting thus means what it always has meant: the demonstration of an *actual*, as opposed to merely a *potential*, conflict.

This reading is amply confirmed by *Geier*, which explicitly referred to "clear evidence" in discussing conflict preemption. Specifically, this Court reasoned that conflict preemption "turns on the identification of 'actual conflict[]'" and then explained that "a court should not find pre-emption too readily in the absence of *clear evidence* of a *conflict*." 529 U.S. at 884-85 (emphasis added).

In referring to "clear evidence," the Court in *Geier* cited a portion of its previous decision in *English*. The discussion addressed whether a federal statute protecting whistleblower employees in the nuclear power industry against retaliation (and establishing and defining an administrative remedy in the Department of Labor) preempted a state-law tort claim for intentional infliction of emotional distress based on the same alleged retaliation. In arguing for preemption, the employer maintained that the

availability of a state remedy with a longer statute of limitations and the potential for recovery of exemplary damages would reduce the incentive for whistleblowers to utilize the federal administrative remedy and thus result in fewer safety violations being brought to federal regulators' attention – so that the safety of nuclear facilities would be diminished. Although this Court agreed there was "some force to this argument," it was insufficient to establish conflict preemption. The Court explained:

> First, many, if not most, retaliatory incidents come about as a response to safety complaints that employees register with federal regulatory agencies. The Federal Government thus is already aware of these safety violations, whether or not the employee invokes the [federal] remedial provision[] * * * . Also, we are not so sure as respondent seems to be that employees will forgo their [federal remedial] options and rely solely on state remedies for retaliation. *Such a prospect is simply too speculative a basis on which to rest a finding of pre-emption.* The Court has observed repeatedly that pre-emption is ordinarily not to be implied absent an 'actual conflict.' See, *e.g.*, *Savage v. Jones*, 225 U.S. 501, 533 (1912). The 'teaching of this Court's decisions * * * enjoin[s] seeking out conflicts between state and federal regulation where none *clearly* exists.' *Huron Portland Cement Co. v. Detroit*, 362 U.S. 440, 446 (1960).

English, 496 U.S. at 90 (emphasis added). Notably, the manufacturer in *English* provided no data or other evidence to support its prediction that whistleblowers would abandon federal administrative remedies

merely because they could *also* use a more favorable state judicial remedy. See Resp. Br. 44-45, *English* v. *General Electric Co.* (1990) (No. 89-152), 1990 WL 505669.

As the foregoing makes clear, the references to "clear evidence" in *Geier* and "clear" conflicts in *English* are thus nothing more than a restatement of the basic principle that, for the Supremacy Clause to come into play, there must be an "actual," and not merely a potential, conflict between federal and state requirements. It is not enough for the proponent of a conflict preemption argument to predict (without supporting data or evidence) what future actions of third parties might be – that type of prediction is simply too "speculative" to establish the requisite conflict between federal and state law. Nothing in *Geier* and *English* remotely supports the establishment of a "clear and convincing" burden of proof.

What is more, if the Court in *Levine* had meant to require more than the "clear" evidence of a conflict required in *Geier* and *English* – if it had meant to create a special ("clear and convincing") standard of proof unique to prescription drug labeling cases – then it surely would have said so. The Court, like Congress, "does not * * * hide elephants in mouseholes." *Whitman* v. *Am. Trucking Ass'ns., Inc.*, 531 U.S. 457, 468 (2001). As noted above, no one asked this Court in *Levine* to adopt a heightened standard of proof for conflict preemption – and, indeed, no such standard was necessary to resolve the case because the defendant there provided "no * * * evidence" FDA "would not have approved a [labeling]

change" that would have added "the kind of warning required by the Vermont jury." 555 U.S. at 571-72.

Finally, the Third Circuit's reading of *Levine* is especially implausible for an additional reason. In *Geier* itself, the Court expressly *rejected* an argument that a defendant must shoulder a "special burden" in certain subcategories of implied preemption cases. 529 U.S. at 870-74. Such a "special burden," the Court explained in words that are equally applicable to the Third Circuit's holding, "find[s]" no "basis * * * in this Court's precedents" and would "promise practical difficulty by further complicating well-established pre-emption principles that already are difficult to apply." *Id.* at 872-73. In light of that holding, *Geier*'s reference to "clear evidence" obviously did not alter the ordinary burden of persuasion in establishing conflict preemption. Nor is it plausible to conclude that this Court in *Levine* intended to adopt the very kind of "special burden" rejected in *Geier* (and without even mentioning this aspect of that decision).

In reversing the decision below, this Court should make clear that its reference to "clear evidence" in *Levine* was *not* intended to adopt a heightened burden of proof. Instead, the Court should explain that it was merely declaring, as it has done in past conflict-preemption cases, that preemption requires demonstrating an actual, as opposed to merely a potential or hypothetical, collision between federal and state law. In this setting, that translates into the requirement of a showing that it is more likely than not FDA would have rejected the warning the plaintiff claims should have been given. Such clarification would send a strong signal to the lower courts that there is no need to create special, complicated rules

for different categories of evidence (*e.g.*, warnings proposed by citizen petitions versus by manufacturers). Instead, *any* type of proof demonstrating that FDA would have rejected a warning suffices to establish preemption.

II. THE QUESTION WHETHER FEDERAL LAW PRECLUDED A PRESCRIPTION DRUG MANUFACTURER FROM ALTERING ITS LABELING IS PROPERLY RESOLVED BY THE COURT, NOT BY A JURY

Not only did the Third Circuit misread *Levine* in imposing on pharmaceutical manufacturers an unwarranted "clear and convincing evidence" burden of proof. Equally problematically, it also held that whether FDA would have rejected a proposed warning is a *fact* question *for the jury*, even when (as in this case) the historical facts are undisputed. Pet. App. 36a-37a, 46a-47a n.122, 54a-55a. Under that approach, issues of conflict preemption in cases involving prescription drugs would routinely be relegated to a jury even where the regulatory record clearly shows it is more likely than not FDA would have rejected the proposed warning. See Pet. i, 28; Pet. App. 59a-60a. The Third Circuit erred in holding that this issue was for the jury, not the court.

As petitioner and the Solicitor General demonstrate, the Third Circuit was clearly wrong to apply that approach in this case. Unlike in *Levine*, this case involved an *actual* FDA decision to reject a warning concerning the risk at the center of respondents' claim. As petitioner and the Solicitor General show, the meaning and effect of FDA's

decision to reject the proposed labeling presents a *legal* question for the court, not a factual question for a jury. Pet. Br. 22-24, 42-45; U.S. Inv. Br. 13-16. The question is "properly determined as a matter of law from FDA's Complete Response Letter, read in the context of petitioner's underlying labeling supplement and the surrounding regulatory framework and related FDA actions." U.S. Inv. Br. 15. And "[e]ven if disputed subsidiary factual questions were relevant to determining the meaning and effect of the agency's 2009 decision, the ultimate inquiry would remain a legal one." *Ibid.*

Although this rationale would suffice to reverse the decision below, PLAC and the Chamber urge the Court to go further and make clear that in all cases involving prescription drug manufacturers, issues of conflict preemption – including questions concerning whether the FDA would have rejected a warning the manufacturer never proposed – are issues that should be resolved by courts, not juries.

In concluding otherwise, the Third Circuit took the view that the proper decisionmaker with respect to such "counterfactual" scenarios was somehow left open in *Levine*. Pet. App 39a-40a & n.102. In fact, the Vermont trial court unambiguously held that "[p]reemption is an issue *for the Court*, not the jury" – and it relied on that holding in making its own findings and resolving defendant's post-trial motion for judgment based on new documentary evidence (correspondence with FDA) not presented at trial. *Levine* v. *American Home Products*, 2004 WL 5456809 (Vt. Super. Ct. July 30, 2004) (emphasis added). In affirming, the Vermont Supreme Court in no way questioned that holding, and indeed both the majority

and dissent treated the preemption issue (including the embedded question of what the FDA would have done) as one for the court. Thus, both state courts resolved the issue for themselves, without relying on any jury finding or requiring that the issue be resolved by a jury. And so, too, did this Court, as the Third Circuit was constrained to admit. See Pet. App. 39a-40a (acknowledging that this Court "did decide that the evidence presented in [*Levine*] was not sufficient to pass the clear evidence test").

Thus, every court involved in *Levine* treated the question of whether the FDA would have approved the warning sought by plaintiff as one for the court to resolve. And, not surprisingly, in the decade since *Levine* was decided, "[m]any other circuits have followed this approach" in resolving the conflict preemption issue in prescription drug cases. Pet. App. 40a. *Levine* itself thus strongly supports treating the embedded issue of what FDA would have done as one properly resolved by courts, not juries.

This approach also fits comfortably within the traditional framework for resolving conflict-preemption issues. As this Court has long made clear, conflict preemption flows directly from the text of the Supremacy Clause, which provides: "This Constitution, and the Laws of the United States * * * and all Treaties * * * shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const. art. VI, cl. 2. See *Brown* v. *Hotel & Restaurant Employees & Bartenders Int'l Union Local 54*, 468 U.S. 491, 501 (1984) (state and local laws that conflict with federal law are preempted "by direct

operation of the Supremacy Clause"). This Court's general methodology in resolving conflict preemption issues is well settled: "Deciding whether a state statute is in conflict with a federal statute and hence invalid under the Supremacy Clause is essentially a two-step process of first ascertaining the construction of the two statutes and then determining the constitutional question whether they are in conflict." *Perez* v. *Campbell*, 402 U.S. 637, 644 (1971). See also note 6, *supra*. Plainly, each of these steps in the overall conflict-preemption analysis involves the determination of an issue of law.

The appropriateness of *judicial* resolution of issues relating to conflict preemption is confirmed by both the history and form of the Supremacy Clause. During the Convention, the Framers considered "three mechanisms for resolving conflicts between federal and state law." Bradford Clark, *Separation of Powers As a Safeguard of Federalism*, 79 TEX. L. REV. 1321, 1348 (2001). The two primary options were (1) a "congressional negative," included in the Virginia Plan, which would have expressly authorized Congress to nullify state laws that, in Congress's judgment, were contrary to the Constitution (or, in a later version, "improper" for any reason), and (2) the Supremacy Clause, included in the New Jersey Plan, which assigned *to the courts* in the first instance the duty to ensure that state laws that were inconsistent with federal laws would be accorded no effect (and preempted). See Bradford Clark, *Unitary Judicial Review*, 72 GEO. WASH. L. REV. 319, 325-27 (2003); Viet Dinh, *Reassessing The Law of Preemption*, 88 GEO. L.J. 2085, 2089-90 (2000); see also Amicus Br. of the U.S. Chamber of Commerce, *Wyeth* v. *Levine*, 2008 WL 2322235 (2008) (No. 06-1249), at *14-*18

(discussing genesis of Supremacy Clause). Moreover, the text and structure of the Supremacy Clause – with its second clause expressly directed at "Judges" and its third clause in the form of a *non obstante* provision (which was widely understood as a directive governing judicial interpretation) – confirm the appropriateness of conflict preemption issues being resolved by judges, not juries. See *PLIVA* v. *Mensing*, 131 S. Ct. 2567, 2579-80 (2011) (plurality); see also Caleb Nelson, *Preemption*, 86 VA. L. REV. 225, 232, 235-44, 292-303 (2000).

Despite a setting that clearly points toward *judicial* resolution of the Supremacy Clause's meaning, and the resolution by all three courts in *Levine* of the conflict preemption issue without any suggestion that it was properly for the jury, the Third Circuit took pains to tease out and isolate the "counterfactual" question of what "the FDA would have done" from its context and concluded that, viewed in isolation, that question presented an issue of "fact" for the jury. See Pet. App. 38a-55a.[8] The

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[8] Compare Robert Strassfeld, *If . . . : Counterfactuals in the Law*, 60 GEO. WASH. L. REV. 339, 340-41 (1992) ("[W]hen we talk about what might have been but did not happen, we leave the domain of facts * * *. Whatever status we give to these imaginative creations, we are certain that they differ in kind from facts."); Amy Burns, *Counterfactual Contradictions: Interpretive Error in The Analysis of AEDPA*, 65 STAN L. REV. 203, 211 (2013) ("[Counterfactuals] are commonplace *legal* questions without which adjudication as we know it would not be possible. Courts do this day in and day out * * * [T]he practice sweeps across divergent areas of the law.") (emphasis added); Gerald Magliocca, *Introduction: "What if" Counterfactuals in Constitutional History*, 45 IND. L. REV. 1, 1 (2011) ("Counterfactual reasoning is a staple of legal analysis.").

Third Circuit acknowledged that this supposedly factual issue did not involve any question of *historical* fact but rather called for a prediction about what the expert federal agency, FDA, would have done under circumstances that never actually occurred. In the Third Circuit's view, however, that prediction raised an issue of fact requiring an "evaluative inference" that was "based on correspondence, agency statements, contemporaneous medical literature, the requirements of the CBE regulation, and *whatever intuitions the factfinder may have about administrative inertia and agency decision-making processes.*" Pet. App. 54a (emphasis added). "This assessment," the Third Circuit opined, "is certainly complex, but it does not require any special legal competence or training." *Ibid.*

This analysis is flawed. Whether this issue is properly characterized as one of fact, law or something else entirely (or a mixed question of law and fact), it plainly calls upon the decisionmaker to understand the complex backdrop of FDA's regulations and procedures, including the standards the agency applies to determine whether there is a sufficient scientific basis to provide additional warnings (and other cautionary statements) in various parts of the highly regulated drug labeling. It may also, as here, require the decisionmaker to understand how the agency addresses concerns regarding the appropriate wording of proposed labeling changes. See U.S. Inv. Br. 5-6, 19-22. In addition, the decisionmaker, again as in this case, may have to interpret FDA decisions and communications, which are properly "read in the context of [the manufacturer's] underlying labeling supplement and the surrounding regulatory framework and related FDA actions." *Id.* at 15. And

yet, as the Solicitor General explains, "[e]ven if disputed subsidiary factual questions were relevant to determining the meaning and effect of the agency's 2009 decision, the ultimate inquiry would remain a legal one." *Ibid.*

In other settings that call for predictive determinations about what other institutional decisionmakers *would have done* under circumstances that did not actually occur, courts have themselves often determined the answer as a matter of law. This is true even in legal settings that do not so clearly call for judicial decision-making as does applying the Supremacy Clause to issues of implied conflict preemption. For example, "[w]hen appellate courts review an error in a criminal trial to determine if it was harmless, they must pretend that the error never happened and ask themselves if the jury would have acquitted the defendant." Magliocca, *supra*, 45 IND. L. REV. at 1. Similarly, when courts conduct a severability analysis, they ask whether Congress would have enacted the same statute if it knew that one or more portions would be invalidated. See *Murphy* v. *National Collegiate Athletic Ass'n*, 138 S. Ct. 1461, 1482 (2018); see also *id.* at 1485 (Thomas, J., concurring) ("The Court must make this severability determination by asking a counterfactual question: 'Would Congress still have passed the valid sections had it known about the constitutional invalidity of the other portions of the statute?'") (internal quotation marks omitted). Accordingly, there is nothing unusual about judges, rather than juries, deciding counterfactual issues in the context of preemption issues under *Levine*. And, of course, that approach would avoid the host of potential practical problems – in particular, the risk of non-uniform outcomes not

susceptible to appellate correction and reconciliation – that would flow from treating the counterfactual issue as a factual question for lay juries.

III. THE THIRD CIRCUIT'S REASONING ALSO IGNORES THIS COURT'S PRE-EMPTION TEACHINGS AND, IF LEFT UNCORRECTED, WILL CREATE HARMFUL CONSEQUENCES

There are several additional reasons why this Court should reverse and, in so doing, expressly reject the Third Circuit's analysis (rather than resolving the case on narrower grounds that might leave the decision below intact for other types of pharmaceutical cases). Under the decision below, a manufacturer cannot prevail on the preemption argument pre-trial, as a matter of law, unless there is a "smoking gun" rejection letter from FDA that would leave a jury no choice but to find the claim preempted. Moreover, so long as a plaintiff can conjure up some variation between the wording of the warning rejected by FDA and the wording plaintiff says should have been proposed, preemption can be defeated or at least delayed until trial (where it will be decided by a jury). These outcomes strip the constitutional preemption defense of much of its practical utility and render it susceptible to being circumvented or effectively rendered meaningless. The Third Circuit's highly restrictive two-part gloss on *Levine* ignores this Court's teachings in several cases and, if affirmed, will have multiple negative effects.

a. *Preemption's Value as a Threshold Legal Issue.* In most settings, courts treat preemption as an issue capable of resolution on purely legal grounds at the

threshold of or early in litigation (typically on a motion to dismiss or for summary judgment). Much of the practical benefit of the doctrine stems from its capacity to ensure that litigants are not forced to endure lengthy and costly discovery proceedings, and even trial, defending against state-law claims that violate the Supremacy Clause.

This Court has recognized the need to preserve this salutary function of preemption – and to prevent the defense from being circumvented through artful pleading. Thus, where preemption hinges on the allegations of a complaint, the Court has repeatedly stated that plaintiffs may not avoid preemption through artful pleading. See, *e.g.*, *Aetna Health Inc.* v. *Davila*, 542 U.S. 200, 214 (2004) ("[D]istinguishing between pre-empted and non-pre-empted claims based on the particular label affixed to them would 'elevate form over substance and allow parties to evade' the pre-emptive scope of ERISA simply 'by relabeling their contract claims as claims for tortious breach of contract.'") (quoting *Allis-Chalmers Corp.* v. *Lueck*, 471 U.S. 202, 211 (1985)); *Chicago & N.W. Transp. Co.* v. *Kalo Brick & Tile Co.*, 450 U.S. 311, 324 (1981) ("[C]ompliance with the intent of Congress cannot be avoided by mere artful pleading."). To hold otherwise would deprive a defendant of the right to obtain the dismissal of preempted claims at the pleading stage.

The Third Circuit's decision similarly allows a plaintiff to avoid both dismissal and summary judgment merely by arguing FDA's decision rejecting a warning about the risk in question *might* have been different if the warning had been worded only slightly differently. But it is no more difficult to conjure up

hypothetical alternative wordings for a warning than it is to use artful pleading in a complaint. The Third Circuit's flawed approach also forces a trial in many if not all cases where no warning was ever sought to be added by a defendant (because, for example, the risk was totally unsubstantiated). Taken together, the "clear and convincing" standard of proof and the jury aspects of the Third Circuit's decision will allow plaintiffs to evade preemption through artful rephrasing of warnings and will deprive the constitutional defense of most of its value at the dismissal and summary judgment stages in pharmaceutical cases.

b. *This Court's Teachings in* PLIVA *and* Bartlett. In other settings, the Court has not hesitated to make clear that preemption is an important constitutional defense that may not be defeated by mere speculative possibilities or by arguments that could be made in every case. Thus, in *PLIVA, Inc.* v. *Mensing*, 564 U.S. 604 (2011), the Court rejected the argument that a generic drug manufacturer (which is obligated by federal law to use the same labeling as the brand-name drug) could have asked FDA to change both its own and the brand-name label, and such a request might ultimately have resulted in FDA's permitting the change. *Id.* at 618-22. Because the manufacturer had not even *tried* to persuade FDA to do so, plaintiffs contended, the manufacturer could not establish conflict preemption. This Court emphatically rejected that argument, explaining that "[i]f these conjectures suffice to prevent federal and state law from conflicting for Supremacy Clause purposes," then conflict preemption would be rendered "largely meaningless." *Ibid.*

Similarly, in *Mutual Pharmaceutical Co.* v. *Bartlett*, 570 U.S. 472 (2013), the Court rejected plaintiff's contention that a drug manufacturer could avoid the direct conflict between federal and state law merely by electing to stop selling the medication altogether. Accepting that argument, which could be made in virtually every case, the Court explained, would render impossibility preemption "meaningless." *Id.* at 488. The Third Circuit did not explain how its decision to relegate to *the jury* an equally speculative hypothetical scenario, based on alternative wording for a warning that virtually any plaintiff could claim, can be squared with *PLIVA* and *Bartlett*. In fact, it cannot.

c. *Burdens on the FDA.* The Third Circuit's flawed approach would likely also burden the federal regulatory process governing drug labeling. The decision creates powerful incentives for drug manufacturers to constantly propose labeling changes to FDA to ensure that plaintiffs cannot defeat preemption by invoking hypothetical alternative language.

In *Buckman Co.* v. *Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), which held that fraud-on-the-FDA claims are impliedly preempted, this Court emphasized the need to avoid such unwarranted burdens on FDA's regulatory processes. Specifically, the Court explained the negative impact such claims would have on the agency's approval of certain categories of medical devices:

> [F]raud-on-the-FDA claims would also cause applicants to fear that their disclosures to the FDA, although deemed appropriate by the Administration, will later be judged insufficient

> in state court. Applicants would then have an incentive to submit a deluge of information that the Administration neither wants nor needs, resulting in additional burdens on the FDA's evaluation of an application. As a result, the comparatively speedy [approval] process could encounter delays * * * .

531 U.S. at 351. In much the same way, the Third Circuit's flawed approach to conflict preemption, if affirmed, would multiply the burdens on FDA's oversight of drug labeling.

d. *Effects on Drug Development and the Rising Tide of Pharmaceutical Litigation.* Developing drugs is very expensive. See, *e.g.*, J.A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, at 5 (Nov. 18, 2014) (estimated average industry cost of new prescription drug approval, including failures and capital costs, is $2.59 billion). A manufacturer will not invest the vast sums necessary to develop a drug unless it believes it can recoup its investment. Allowing failure-to-warn claims to proceed under the varying tort laws of the fifty states despite a preponderance of the evidence that FDA would not have approved the proposed warnings would impose significant and unpredictable defense and liability costs on manufacturers, and thereby reduce their willingness to invest in drug development. See *Caplinger* v. *Medtronic, Inc.*, 784 F.3d 1335, 1346 (10th Cir. 2015) (Gorsuch, J.) (discussing medical devices). The Third Circuit's approach, if affirmed, would increase the costs and uncertainty of litigation faced by manufacturers by requiring more trials and placing the preemption issue in the hands of lay juries. Given the rapid

expansion in recent years of federal litigation against pharmaceutical companies (see note 4, *supra*), this is no idle concern.

CONCLUSION

For the foregoing reasons, the judgment should be reversed.

Respectfully submitted.

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Supreme Court of the United States

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

DORIS ALBRECHT, ET AL.,
Respondents.

On Writ of Certiorari to the
United States Court of Appeals for the Third Circuit

BRIEF OF AMICUS CURIAE PUBLIC CITIZEN IN SUPPORT OF RESPONDENTS

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INTEREST OF AMICUS CURIAE[1]

Public Citizen is a non-profit consumer advocacy organization with members and supporters in every state. Since its founding in 1971, Public Citizen has assessed the safety and efficacy of drugs, provided information on drug safety to the public, and advocated before the Food and Drug Administration (FDA) for product labeling and regulation to reduce safety risks. In June 2013, a Public Citizen report compiled a list of drugs for which black-box warnings—the most serious contraindications and warnings—were added after a generic equivalent entered the market. Looking at a five-year period, the report identified 53 drugs for which a black-box warning calling attention to serious or life-threatening risks was added after generic market entry. The data underscore the public health imperative of requiring pharmaceutical companies to maintain active surveillance of safety.

In both this Court and the lower courts, Public Citizen has participated as amicus in many cases brought by patients injured by drugs that carried inadequate warnings. Patients and physicians depend on brand-name manufacturers to provide adequate warnings for prescription drugs. Allowing patients to pursue tort claims against pharmaceutical manufacturers for injuries caused by inadequate warnings is important as both an incentive for manufacturers to be vigilant about product safety and a means to provide remedies to patients. For this reason, this case has important implications that go well beyond the interests of the parties.

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[1] This brief was not authored in whole or part by counsel for a party. No one other than amicus curiae Public Citizen made a monetary contribution to preparation or submission of the brief. Counsel for all parties have consented in writing to the filing of this brief through blanket consents on file with the Court.

SUMMARY OF ARGUMENT

I. The Food, Drug, and Cosmetic Act (FDCA), as this Court has explained, was enacted "to bolster consumer protection against harmful products." *Wyeth v. Levine*, 555 U.S. 555, 574 (2009) (citing *Kordel v. United States*, 335 U.S. 345, 349 (1948), and *United States v. Sullivan*, 332 U.S. 689, 696 (1948)). When enacting this consumer protection law, however, Congress did not create a federal remedy for consumers harmed by unsafe or ineffective drugs. To the contrary, Congress rejected a provision that would have created a damages remedy, *see* H.R. 6110, 73d Cong., 1st Sess. § 25 (1933), specifically because state law already provided one, *see Wyeth*, 555 U.S. at 574 & n.7. Indeed, "[c]ourts entertained tort suits against [drug] manufacturers since well before the passage" of the FDCA, and such litigation has long been a "common feature of the legal landscape." *Bates v. Dow AgroSciences LLC*, 544 U.S. 431, 441 (2005) (discussing pesticides).

Against this background and the principles established by this Court's preemption jurisprudence, *Wyeth* provides a clear framework for deciding this case. Federal regulations task a brand-name drug manufacturer with primary responsibility for keeping its product labeling up to date, and they provide the manufacturer with the flexibility to do so. Here, Merck did not update its labeling until ordered to do so by the FDA, years after Merck became aware of evidence that Fosamax was associated with a risk of atypical femoral fractures. Under *Wyeth*, Merck cannot bear the burden of showing that, had Merck added a warning about atypical femoral fractures before 2010, the FDA would have rejected the updated warning of this risk—known to physicians as "Fosamax fractures." JA448.

II. Merck and its amicus curiae PhRMA, however, suggest that the Food and Drug Administration Amendments Act of 2007 (FDAAA) altered the regulatory scheme under which this Court decided *Wyeth*. In fact, the 2007 law reinforced *Wyeth*'s central premise: that prescription drug manufacturers have primary responsibility for keeping drug labeling updated and that, therefore, "absent clear evidence that the FDA would not have approved a change" to the drug's label, the Court "will not conclude that it was impossible for [the manufacturer] to comply with both federal and state requirements." *Wyeth*, 555 U.S. at 571.

Notwithstanding that most labeling changes are initiated by manufacturers, Merck and PhRMA argue that the Court should infer here the FDA would not have permitted any update to the Warnings or Precautions sections to advise physicians and patients about atypical femoral fractures. They argue that, under the FDAAA, the FDA is required to order labeling changes where warranted and, thus, if the FDA has not ordered a change, none was warranted. As applied to the facts here, their theory is that, when the FDA did not approve the *stress* fracture warning proposed in 2009, it signaled that no warning concerning *atypical* fractures would be permitted. The theory is illogical, speculative, and undercut by the facts of this case.

III. State law has long recognized that federal regulation has a role in products liability cases, because compliance with federal regulation is relevant to establish whether the manufacturer acted reasonably. Regulatory compliance is both a strong defense to a state-law tort claim and a reflection of the fact that juries have long been charged with considering the actions of federal regulators, including the FDA. This case presents no

ground for shifting the longstanding role of factfinders in deciding factual disputes underlying legal claims and defenses.

ARGUMENT

I. The standard stated by this Court in *Wyeth* governs the preemption analysis here.

A. Consideration of preemption of state-law claims seeking damages for injuries caused by prescription drugs begins with this Court's decision in *Wyeth*. And understanding of *Wyeth* begins with the longstanding "cornerstones of [the Court's] pre-emption jurisprudence." *Wyeth*, 555 U.S. at 565.

> First, "the purpose of Congress is the ultimate touchstone in every pre-emption case." *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (internal quotation marks omitted); *see Retail Clerks v. Schermerhorn*, 375 U.S. 96, 103 (1963). Second, "[i]n all pre-emption cases, and particularly in those in which Congress has 'legislated ... in a field which the States have traditionally occupied,' ... we 'start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress.' " *Lohr*, 518 U.S., at 485 (quoting *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947)).

Wyeth, 555, U.S. at 565.

Because the cornerstones are familiar, it is easy to skip over them. The Court has reiterated them time and again, however, because they embody important principles of the Nation's federal scheme: As Justice Thomas wrote in *Wyeth*, "to ensure the protection of our fundamental liberties, the Constitution establishes a system of dual

sovereignty between the States and the Federal Government." *Id.* at 583–84 (Thomas, J., concurring in the judgment) (quoting *Atascadero State Hospital v. Scanlon*, 473 U.S. 234, 242 (1985) (internal quotation marks omitted), and *Gregory v. Ashcroft*, 501 U.S. 452, 457 (1991) (internal quotation makers omitted)). The States are "independent sovereigns in our federal system." *Id.* at 566 n.3 (majority opinion). Thus, "in protecting our constitutional government, 'the preservation of the States, and the maintenance of their governments, are as much within the design and care of the Constitution as the preservation of the Union and the maintenance of the National government.'" *Id.* at 585 (Thomas, J., concurring) (quoting *Texas v. White*, 7 U.S. 700, 725 (1868)).

The preemption touchstones—Congress's legislative purpose and the presumption against preemption—thus derive from core constitutional principles. Accordingly, out of respect for the states' sovereignty and their traditional role in protecting the health and safety of their citizens, the Court assumes that "Congress does not cavalierly pre-empt state-law causes of action." *Lohr*, 518 U.S. at 485.

B. Although the drug provisions of the FDCA have been amended many times since 1938, including significant amendments in 1962, 1984, 1997, 2007, and 2012, arguments that products liability suits (whether based on design or labeling) against drug manufacturers were preempted by the FDCA were seldom made and, until the mid-2000s, rarely successful.[2] Significantly, in

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[2] *See, e.g.*, *Tobin v. Astra Pharm. Prods., Inc.*, 993 F.2d 528, 537 (6th Cir. 1993) (no preemption); *Osburn v. Anchor Labs.*, 825 F.2d 908, 911–13 (5th Cir. 1987) (same); *Wells v. Ortho Pharm. Corp.*, 788

1962, when Congress amended the FDCA to require, for the first time, that drug manufacturers demonstrate effectiveness in addition to safety prior to receiving marketing approval, *see Wyeth*, 555 U.S. at 567, Congress addressed preemption only to state that the new provisions do *not* preempt state law.[3]

Later, beginning in 1976, Congress enacted provisions expressly preempting categories of state laws with respect to other FDA-regulated products, including foods, medical devices, and cosmetics. *See* 21 U.S.C. §§ 343-1(a), 360k(a), & 379s. As these preemption provisions reflect, Congress has been particularly attentive to federalism concerns in connection with regulation under the FDCA and has crafted provisions to address these concerns where, in Congress's view, those changes were appropriate. Yet Congress never enacted a provision preempting state law concerning prescription drugs, much less a provision directed at state-law damages suits.

Against this backdrop, and the Court's longstanding touchstones of preemption analysis, the Court in *Wyeth* rejected the notion that "obstacle" conflict preemption bars state-law claims brought against brand-name drug manufacturers for injuries caused by inadequate labeling of their products. 555 U.S. at 573; *id.* at 604 (Thomas, J., concurring in the judgment) (rejecting notion of obstacle

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F.2d 741, 746 (11th Cir. 1986) (same); *Feldman v. Lederle Labs.*, 592 A.2d 1176, 1195–97 (N.J. 1991) (same).

[3] *See* Pub. L. No. 87-781, § 202 (1962) ("Nothing in the amendments made by this Act to the federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law.").

preemption). At the same time, while not ruling out the possibility that "impossibility" conflict preemption might apply in some instances, the Court held that the manufacturer had failed to carry its burden of establishing impossibility in that case. *Id.* at 571; *see also id.* at 593 (Thomas, J., concurring).

Wyeth's holding with respect to impossibility preemption of a state-law claim based on the failure to provide an adequate warning in drug labeling is straightforward: "[A]bsent clear evidence that the FDA would not have approved a change to [the] label" to include the warning, the Court "will not conclude that it was impossible for [the manufacturer] to comply with both federal and state requirements." *Id.* at 572. And absent an "affirmative decision" by the FDA, such clear evidence is lacking. *Id.* at 571.

This approach follows directly from the regulatory scheme. Since 1938, the manufacturer of a new prescription drug must obtain prior approval from the FDA before the drug can be marketed, including approval of each use for which the manufacturer intends to market it. As the parties' briefs explain, to obtain marketing approval, a drug company must first submit a new drug application (NDA) for the FDA's review. 21 U.S.C. § 355(a), (b). If, after reviewing the application, the FDA concludes that the drug is safe and effective for its intended use or uses and that the labeling is not false or misleading, the FDA will send an approval letter to the applicant. *Id.* §§ 355(c)(1)(A), 355(d). FDA approval includes approval of the labeling, which must include several sections, including contraindications, warnings, precautions, and adverse reactions. 21 C.F.R. §§ 201.56, 201.57, 201.80.

Nonetheless, "[m]any serious [adverse drug reactions] are discovered only after a drug has been on the market

for years." Karen Lasser, *et al.*, *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 JAMA 2215, 2218 (May 1, 2002); *see* Jean Lester, et al., *Evaluation of FDA safety-related drug label changes in 2010*, 22 Pharmacoepidemiology and Drug Safety 302, 304 (2013) (stating that "[t]he most critical safety-related label changes" were made "a median 10 and 13 years after drug approval"). To monitor adverse reactions, the FDA requires companies to submit "adverse event reports" to the agency, describing both "serious and unexpected" reactions and less serious ones. *See* 21 C.F.R. § 314.80(c)(1), (2). In this way, federal regulations put the onus of postmarketing surveillance on drug manufacturers, not on the FDA.

In addition, as *Wyeth* discussed, federal regulations impose on manufacturers a continuing responsibility "to maintain their labeling and update the labeling with new safety information." 73 Fed. Reg. 49603, 49605 (Aug. 22, 2008); *see Wyeth*, 555 U.S. at 570–71. A manufacturer can make certain post-approval labeling changes only with prior FDA approval, 21 C.F.R. § 314.70(b), but no prior approval is required for changes "[t]o add or strengthen a contra-indication, warning, precaution, or adverse reaction," *id.* § 314.70(c)(6)(iii), among other things, *id.* §§ 314.70(c), (d). A company's obligation to provide physicians and patients with up-to-date warnings and precautions continues as long as the product is marketed. 21 C.F.R. §§ 201.57(c)(6), 201.80(e). As *Wyeth* noted, "[t]he FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge." 555 U.S. at 1202; *see also, e.g.*, *id.* at 1202 n.11 (citing studies showing that FDA resources are inadequate to its regulatory responsibilities).

In light of the regulatory scheme, and reinforced by the reality that manufacturers initiate the majority of labeling updates, this Court held in *Wyeth* that FDA approval of prescription drug labeling does not immunize a brand-name drug manufacturer from liability for failure to warn. Rather, absent a clear showing that the FDA would not allow a warning that state law requires, compliance with both federal and state law is not impossible, and federal regulation does not preempt patients' state-law claims.

Merck has not made that showing here.

II. The Food and Drug Administration Amendments Act of 2007 does not alter the preemption analysis.

Petitioner Merck and its amicus curiae PhRMA argue that, in light of the FDAAA, the FDA's rejection of a particular manufacturer-suggested labeling change necessarily connotes the FDA's "considered judgment" that *no* change should be made at all. PhRMA Br. 4. In *Wyeth*, this Court considered and rejected a similar argument that regulation under the FDCA—including the FDCA as amended by the FDAAA—establishes both a floor and a ceiling for drug regulation. As the Court said at that time, "[t]he most glaring problem with this argument is that all evidence of Congress' purposes is to the contrary." *Wyeth*, 555 U.S. at 574.

A. *Wyeth* considered and addressed the effect of the FDAAA on analysis of federal preemption of state-law labeling claims, which was enacted after the relevant events in *Wyeth* but before the Court decided *Wyeth*. As the Court's opinion makes clear, the FDAAA did not alter the essential premises that underlie its holding: manufacturers' responsibility for labeling and their authority to make changes without prior approval.

The FDAAA gave the FDA additional resources for drug safety and new authority to compel manufacturers to make labeling changes based on safety information that becomes available after a drug's initial approval. *See* 21 U.S.C. § 355(o)(4)(A). Nonetheless, "the resources of the drug industry to collect and analyze postmarket safety data vastly exceed the resources of the FDA." 153 Cong. Rec. S11832 (daily ed. Sept. 20, 2007) (Statement of Sen. Kennedy). Indeed, "no matter what [Congress does], they will always have vastly greater resources to monitor the safety of their products than the FDA does." *Id.* Not surprisingly, therefore, even *after* passage of the FDAAA in 2007, the majority of revisions to the "Warnings" and "Precautions" sections of prescription drug labeling are initiated by manufacturers, not by the FDA. *See* Lester, *supra*, at 304 (discussing labeling changes made in 2010).

Consistent with these facts, and as *Wyeth* explains, when Congress in 2007 "granted the FDA this authority [to order labeling changes], it reaffirmed the manufacturer's obligations and referred specifically to the "changes being effected" regulation, 21 C.F.R. § 314.70(c), "which both reflects the manufacturer's ultimate responsibility for its label and provides a mechanism for adding safety information to the label prior to FDA approval," *Wyeth*, 555 U.S. at 571. In addition, as *Wyeth* also explains, Congress rejected a proposed provision "that would have required the FDA to preapprove all changes to drug labels" and instead "adopted a rule of construction to make it clear that manufacturers remain responsible for updating their labels." *Wyeth*, 555 U.S. at 567–68 (citing Senate bill and provision now codified at 21 U.S.C. § 355(o)(4)(I)); *see* 21 U.S.C. § 355(o)(4)(I) (stating that the authority granted to the FDA to initiate labeling changes "shall not be construed to affect the responsibility of the [manufacturer] to maintain its label

in accordance with existing requirements, including ... [21 C.F.R. §] 314.70").

In short, this Court in *Wyeth* both considered and addressed the impact of the FDAAA on preemption of state-law claims, and it correctly rejected the argument that the FDAAA alters the preemption analysis.

B. Merck and its amicus curiae PhRMA suggest that the provision of the FDAAA that grants the FDA authority to require labeling changes when new information is brought to its attention alters the underpinning of *Wyeth*, at least in the circumstances of this case. Under their theory, the FDAAA requires the FDA to order any labeling change that it deems required by available information, and, therefore, when the FDA rejects a proposed labeling change on a topic, it is necessarily rejecting any other change that the manufacturer could have proposed at that time. That argument is not a reasonable construction of the statute.

Nothing in the FDAAA requires the FDA, when presented with a proposed labeling change, to consider any changes other than those proposed to it. And nothing in the FDAAA suggests that an FDA response, when it does not propose a warning of its own, necessarily indicates that the agency has considered and rejected any warning other than the one proposed by the manufacturer. The statute thus does not support the notion that the FDA's rejection of a particular proposed warning constitutes a determination "that no new labeling language is warranted." PhRMA Br. 17. This point is true in particular where the FDA states that the specific proposed change is not supported by "the available literature and postmarketing adverse event reporting," JA511–12, but a manufacturer knows that the literature and reports would support a different proposal. *See* Resp.

Br. 9–10 (describing record evidence of Merck's knowledge of adverse events and studies).

Moreover, tasking the FDA with anticipating and considering all possible labeling changes that might be proposed when it accepts or rejects a particular change proposed by a manufacturer would be impractical. Consistent with the facts as they existed pre-FDAAA, *see Wyeth*, 555 U.S. at 578–79 & n.11, a 2015 report of the Government Accountability Office (GAO) found that the "FDA's lack of reliable, readily accessible postmarket safety data has prevented the agency from publishing required reports in a timely manner and has restricted its ability to conduct systematic oversight." GAO, Drug Safety: FDA Expedites Many Applications, But Data for Postapproval Oversight Need Improvement 22, https://www.gao.gov/assets/680/674183.pdf (Dec. 2015). Further, GAO estimated that the FDA failed to review in a timely manner more than half of the submissions associated with 1,400 postmarket studies of drugs on the market. *Id.* at 23–24.

The FDA, too, recognizes the need for continued reliance on manufacturers to identify hazards and initiate labeling changes. As the FDA advised manufacturers several years after passage of the FDAAA, the agency "does not anticipate that all labeling changes that may be related to safety will be required and reviewed under" the authority granted it by FDAAA. FDA, *Guidance for Industry Safety Labeling Changes—Implementation of Section 505(o)(4) of the FD&C Act* 5 (July 2013), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf. Instead, manufacturers are expected to continue to submit labeling revisions "using standard procedures." *Id.*

Thus, the FDAAA does not alter the preemption analysis. Both before the FDAAA and after, the preemption question, as articulated by this Court, is whether there is "clear evidence that the FDA would not have approved a change" to the drug labeling that a plaintiff alleges was inadequate. *Wyeth*, 555 U.S. at 571. Merck's and (more explicitly) PhRMA's suggestion that the FDA's rejection of one specific proposed warning represents a determination that no new warning was permissible is unsupported by the FDAAA and divorced from the reality of prescription drug labeling and FDA practice.

C. Because the FDAAA does not support the notion that the FDA's rejection of one warning connotes, as a matter of law, a rejection of a substantively different warning, the FDA's rejection of a particular warning subsequent to enactment of the FDAAA presents the same questions that this Court in *Wyeth* held controlled preemption under the FDCA: Does the FDA's action clearly demonstrate that the agency rejected or would have rejected the warning that the plaintiff says that state law requires? Under the circumstances here, the FDA's action cannot be so understood.

As respondents have explained, atypical femoral fractures and stress fractures are distinct; the terms denoting the two types of fractures are neither synonyms nor two ways of describing a similar injury. *See* Resp. Br. 12–13. When the FDA rejected the proposed stress fracture warning in May 2009, it explained that "[d]iscussion of the risk factors for *stress* fractures is not warranted and is not adequately supported by the available literature and postmarketing adverse event reporting." JA511–12 (emphasis added). At the same time, the agency approved a labeling revision to add "low

energy femoral shaft and subtrochanteric fractures" (atypical femoral fractures) to the Adverse Reactions section, JA512—meaning that it found a "basis to believe" that there is a "causal relationship" between Fosamax and those atypical fractures. *See* 21 C.F.R. § 201.57(c)(7).

The FDA's 2009 letter belies Merck's claim that the FDA was rejecting a proposed warning—or any warning—about the risk of atypical femoral fractures. The relevant sentence says that, while the FDA "agrees" that "atypical and subtrochanteric fractures" should be added to the Adverse Reactions section of the labeling, "[Merck's] justification for the proposed Precautions section language is inadequate." Quoting Merck's proposed Precaution language, the FDA explains: "Identification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." JA511. That is, the FDA was rejecting a warning *about stress fractures* because the evidence of *atypical* fractures shown in the literature did not support it. The letter, which explicitly distinguishes between atypical and stress fractures, offers no support for the notion that the FDA was rejecting an atypical fracture warning, much less that it was rejecting any possible atypical fracture warning.

In addition, Merck's position overlooks that the FDA wrote to Merck in 2008 that it was "aware of reports" that patients were suffering atypical femoral fractures and was "concerned about this developing safety signal," JA280—a position in tension with Merck's view that the FDA in 2009 had in mind atypical femoral fractures when it rejected the proposed warning on the ground that

discussion of stress fractures was "not adequately supported" by "adverse event reporting," JA511–12.[4]

The FDAAA does not require the assumption of such FDA incoherence, particularly in the face of an entirely logical alternative. As the FDA explained in rejecting Merck's second attempt to warn of stress fractures rather than the more serious atypical femoral fractures, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with" use of Fosamax. JA566. This FDA response again shows that the agency's rejection in 2009 of the proposed warning about stress fractures cannot reasonably be deemed "clear evidence that the FDA would not have approved" a warning to address atypical femoral fractures—a warning that Merck could have, but never, proposed.

Reinforcing that the FDA's May 2009 rejection of the proposed stress fracture warning did not represent a determination that a possible warning or precaution about atypical femoral fractures was not warranted, the FDA suggested to Merck in April 2009 that Merck forgo further discussion of the warning it had proposed and then work with FDA "to decide on language for a W&P [Warning & Precaution] atypical fracture language, if it is warranted." JA508. The FDA suggested that warning language for atypical fractures could be agreed on soon. *See id.* (stating that the FDA was "hopeful" of agreeing on

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[4] That the FDA was addressing Merck's proposed warning for stress fractures, not a possible warning for atypical femoral fractures that had not been proposed, when it rejected Merck's language as "not adequately supported by the available literature and postmarketing adverse event reporting" is further supported by the fact that "[b]etween 1995 and 2010, scores of case studies, reports, and articles were published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures." Pet. App. 13a.

language "in time to allow that language to be included in the PLR [Physician Labeling Rule] conversion supplement"); JA767 (memo from Merck employee stating that FDA "reminded me that we also need to respond to their request for PLR by June"). These materials are incompatible with the notion that a court could decide, as a matter of law, that the FDA would not permit a warning or precaution concerning atypical femoral fractures.[5]

"The question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 620 (2011). In this case, Merck failed to suggest an atypical femoral fracture warning, and Merck's and the FDA's correspondence about a stress fracture warning cannot reasonably be deemed "clear evidence" that Merck could not warn about the risk of atypical femoral fractures. Accordingly, under this Court's precedents, the patients' state-law claims are not preempted.

III. Where factual disputes exist, juries in tort actions have long been tasked with considering the actions of regulators.

Here, the regulatory record fails as a matter of law to support Merck's claim of impossibility preemption. To the extent that a preemption defense turned on disputes of material fact, however, the Solicitor General's concern that juries would not be qualified to resolve those factual issues, *see* Br. of U.S. at 18–21, is unwarranted.

To begin with, juries have long been charged with evaluating agency actions in the context of tort suits.

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[5] The PLR conversion supplement is the means for revising older labeling to bring it into compliance with a 2006 FDA rule that set forth new requirements for drug labeling.

Under traditional tort law, federal approval of a product for marketing and a manufacturer's compliance with federal requirements for product safety plays a role, often a very powerful role, in products liability cases. Consistent with this tradition, the current law in most states allows a manufacturer that is alleged to have sold a defective product to use compliance with federal standards or regulations as non-dispositive evidence that the product was not defective or that the manufacturer acted non-negligently. *See Restatement (Third) of Torts* § 4(b) (1998); *accord* 63B Am. Jur. 2d *Prods. Liab.* § 1922 (Nov. 2018 update) ("As a general rule, compliance with applicable federal standards is relevant but not conclusive evidence in a products liability case.").[6] As the New Jersey Supreme Court recently put it, "federal regulations are of the utmost significance in determining whether 'a manufacturer satisfied its duty to warn the physician about potentially harmful side effects of its product.'" *In re Accutane Litig.*, __ A.3d __, 2018 WL 4761403, at *25 (N.J. 2018) (quoting *Perez v. Wyeth Labs., Inc.*, 734 A.2d 1245 (N.J. 1999)).

Thus, in New Jersey, for example, state law provides manufacturers with the protection of a *rebuttable* presumption of adequacy of an FDA-approved label

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[6] *See, e.g.*, Ind. Code § 34-20-5-1; Kan. Civ. P. Code Ann. § 60-3304; Tenn. Code Ann. § 29-28-104; Utah Code Ann. § 78B-6-703(2); *Salmon v. Parke, Davis & Co.*, 520 F.2d 1359, 1362 (4th Cir. 1975) (North Carolina law); *O'Neill v. Novartis Consumer Health, Inc.*, 55 Cal. Rptr. 3d 551, 557 (Cal. Ct. App. 2007); *Wagner v. Clark Equip. Co.*, 700 A.2d 38, 50 (Conn. 1997); *Brooks v. Beech Aircraft Corp.*, 902 P.2d 54, 63 (N.M. 1995); *Zacher v. Budd Co.*, 396 N.W.2d 122, 133–34 (S.D. 1986); *MacDonald v. Ortho Pharm. Corp.*, 475 N.E.2d 65, 70–71 (Mass. 1985); *Malek v. Lederle Labs.*, 466 N.E.2d 1038, 1039–40 (Ill. App. Ct. 1984); *Sherman v. M. Lowenstein & Sons, Inc.*, 282 N.Y.S.2d 142, 143–44 (N.Y. App. Div. 1967).

warning. *Id.* (citing N.J. Stat. Ann. 2A:58C-4). "A manufacturer that acts in a reasonable and timely way to update its label warnings with the FDA, in accordance with its federal regulatory responsibilities, will receive the protection of the rebuttable presumption." *Id.* at *26.

Although this aspect of state-law claims goes to the merits, not to preemption, it is pertinent here. States have long recognized the importance of the federal regulatory scheme in assessing the reasonableness of conduct alleged to violate state tort law. And in assessing whether a regulatory compliance defense is meritorious, juries have long been charged with considering the connection between a defendant's conduct, federal regulation, and the regulator's decisions.

In addition, the FDCA itself expressly confers on juries the role of factfinder in civil cases stemming from FDA enforcement actions seeking injunctions for violations of the statute, or for seizure of misbranded or adulterated items, *see* 21 U.S.C. §§ 332(b), 334(b), as well as in criminal prosecutions for violations of the FDCA, *id.* § 333 (providing for criminal penalties); *see also Wyeth*, 555 U.S. at 570 ("the statute contemplates that federal juries will resolve most misbranding claims").

Where factual issues are disputed, our legal tradition tasks juries with resolving them. "This is not a rule specific to [a particular legal issue]; it is simply an application of the more general rule that a 'judge's function' at summary judgment is not 'to weigh the evidence and determine the truth of the matter but to determine whether there is a genuine issue for trial.'" *Tolan v. Cotton*, 572 U.S. 650, 656 (2014) (discussing qualified immunity; quoting *Anderson v., Liberty Lobby, Inc.*, 477 U.S. 242, 249 (1986)). *See, e.g., Ortiz v. Jordan*, 562 U.S. 180 (2011) (although qualified immunity is

generally a question of law, case proceeded to a jury where the defense turned on disputed issues of fact).

No reasoned basis exists for a special rule requiring judges exclusively to take on the role of factfinder for factual disputes that arise in considering a preemption defense. *See Boyle v. United Technologies Corp.*, 487 U.S. 500, 514 (1988) ("whether the facts establish the conditions for the defense is a question for the jury").

CONCLUSION

For the foregoing reasons and the reasons stated in the brief of respondents, the decision below should be affirmed.

Respectfully submitted,

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No. 17-290

IN THE
Supreme Court of the United States

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

DORIS ALBRECHT, ET AL.,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Third Circuit

BRIEF OF PUBLIC LAW SCHOLARS AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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QUESTION PRESENTED

Whether the Food and Drug Administration's initial rejection of Petitioner's request to add certain warnings to the label of its name-brand drug preempted state tort claims by legally barring Petitioner from adding to its label the warnings required by state law?

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INTEREST OF AMICI CURIAE

Amici are public law scholars whose teaching and scholarship has addressed federal preemption of state law.[1] Mindful of the gap that sometimes exists between the academy and the concerns of the bench and bar, we seek to bring our scholarship to bear on the particular preemption questions at issue in this case.

Our scholarly interest in preemption arises from teaching and writing in a variety of related fields, including constitutional law, administrative law, health law, and torts. William W. Buzbee is a Professor of Law at the Georgetown University Law Center. Daniel Farber is the Sho Sato Professor of Law at the University of California, Berkeley School of Law. Daniel Lyons is an Associate Professor at Boston College Law School. Thomas O. McGarity holds the Joe R. and Teresa Lozano Long Endowed Chair in Administrative Law at the University of Texas School of Law. Paul McGreal is a Professor of Law at Creighton University School of Law. Nina Mendelson is the Joseph L. Sax Collegiate Professor

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[1] Pursuant to Supreme Court Rule 37.6, counsel for *amici* represent that they authored this brief in its entirety and that none of the parties or their counsel, nor any other person or entity other than *amici* or their counsel, made a monetary contribution intended to fund the preparation or submission of this brief. At an earlier stage, Lieff Cabraser represented plaintiffs in two cases in the Fosamax MDL, which were administratively terminated pending this Court's decision on Defendants' Petition for Certiorari. These plaintiffs were not subject to the summary judgment order on appeal to this Court and Lieff Cabraser no longer represents them. Pursuant to Rule 37.3(a), counsel for *amici* also represent that all parties have consented to the filing of this brief.

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SUMMARY OF ARGUMENT

This case presents basic questions about the extent to which federal administrative agencies will determine the preemptive impact of federal law on state regulation. The parties and the court of appeals focused on the preemptive intent of the Food and Drug Administration (FDA), which rejected a "prior approval supplement" (PAS) application by Merck to make certain changes to its warning label for the drug Fosamax. They have also focused on the likelihood that the FDA eventually would have rejected a different label change, which Respondents argue state tort law required, had Merck chosen to implement that change through the FDA's "changes being effected" (CBE) procedure. *Amici* submit that both sets of arguments inappropriately reorient the preemption inquiry from *Congress*'s preemptive intent to that of the agency.

This Court's precedents establish two critical points: First, Congress intended broadly to preserve state law, including state tort remedies for failure to warn, as a complement to the Food, Drug, and Cosmetic Act's (FDCA) regulation of warning labels for name-brand drugs. *See Wyeth v. Levine*, 555 U.S. 555, 566-68, 574-75 (2009). *Wyeth* held that state tort remedies were consistent with the FDCA's purposes and objectives, and that it is ordinarily possible to comply both with the Act's labeling regime and state tort duties. *See id.* at 570-73, 574-76. Second, this

Court has made clear that the key question for impossibility preemption—the only sort of preemption argued here—is whether it was "lawful under federal law for the Manufacturers to do what state law required of them." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 618 (2011). The FDA's "complete response letter" denying Merck's initial PAS application is thus relevant *only* to the extent that it would legally foreclose Merck from changing its label through the CBE process.

This brief argues that the PAS denial letter has no such legal effect and thus cannot preempt Respondents' state law claims. Neither Petitioner nor the United States points to any authority indicating that the PAS process, once initiated, forecloses a manufacturer from utilizing the CBE option. The FDA's "complete response letter" cannot itself preempt state claims because it was not final agency action and did not carry the force of law. And in any event the PAS application involved a proposed warning different from the one Respondents allege state law requires.

Nor should the FDA's letter ruling be considered to be "clear evidence that the FDA would not have approved a change to [Fossamax's] label." *Wyeth*, 555 U.S. at 571. *Wyeth* indicated that such a showing would require an actual attempt to change the label under the CBE procedure that the FDA then rejected. *See id.* at 572. Speculation about how the FDA *might* have responded to an application for a different label that Merck never made contravenes *PLIVA*'s insistence that the preemption inquiry not "take into account hypothetical federal action." 564 U.S. at 621 n.6. Moreover, shifting the focus away

from Congress's intent to what the agency *might* have done invites troublesome probabilistic inquiries that raise difficult procedural complications, such as whether preemption must go to the jury or whether plaintiffs should be allowed discovery concerning the FDA's decisionmaking process. And such an inquiry inappropriately puts the agency, not Congress, in charge of preemption.

Any uncertainties regarding Congress's preemptive intent in this case must be resolved in light of this Court's longstanding presumption against preemption. *See Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947). Petitioner's *amici* have used this case to launch a general assault on the *Rice* presumption, and to argue that that presumption is inapplicable in implied conflict preemption cases like this one. This Court has rejected these arguments before, and it should reject them again because *Rice*'s presumption plays an integral role in preserving the autonomy of the states.

ARGUMENT

I. Congress Preserved a Key Role for State Tort Law as Part of its Statutory Scheme for Regulating Name-Brand Drugs.

Petitioner's preemption argument in this case faces an uphill climb. The problem is not simply that this Court applies a general presumption against preemption. *See Rice*, 331 U.S. at 230. Rather, the primary obstacle to Petitioner's argument is that this Court has already interpreted Congress's scheme for regulating the warning labels of name-brand drugs in light of the *Rice* presumption against preemption.

In *Wyeth*, this Court broadly considered the FDCA's labeling regimes for such drugs; it concluded that Congress "took care to preserve state law," 555 U.S. at 567, and that state tort remedies "provided appropriate relief for injured consumers," *id.* at 574. And the Court rejected *both* an impossibility preemption argument and an argument that state-law failure to warn claims conflicted with the "purposes and objectives" of the FDCA. *See id.* at 570-73, 574-76. Those holdings leave only the very narrowest of pathways for a preemption argument in this case—if in fact they leave any pathway at all.

Wyeth's reading of the FDCA carries the "enhanced force" of *stare decisis* that accrues "when a decision . . . interprets a statute." *Kimble v. Marvel Entm't, LLC*, 135 S. Ct. 2401, 2409 (2015); *see also Patterson v. McClean Credit Union*, 491 U.S. 164, 172-73 (1989). This Court's cases make clear that some federal regulatory regimes, such as the National Bank Act, reflect Congress's intent to broadly preempt state law. *See, e.g., Barnett Bank of Marion Cnty., N.A. v. Nelson*, 517 U.S. 25, 32-33 (1996). But Congress intended other federal regimes to preserve much state regulation, and this Court has accordingly tended not to find preemption in those areas. *See, e.g., Pacific Gas & Elec. Co. v. State Energy Res. Conservation & Dev. Comm'n*, 461 U.S. 190, 205-08 (1983) (concluding that federal regime governing safety of nuclear power plants was intended to preserve traditional state authority over public utility regulation). *Wyeth* made clear that the FDCA's prescription drug regime falls into the latter category. That binding construction of the FDCA must inform this Court's resolution of the more specific issues presented in this case.

The FDCA's provisions for regulating name-brand drugs have displayed a conspicuous and consistent concern for preserving state common law claims as part of the regulatory scheme. Congress rejected a proposal to include a private right of action for damages in the 1938 FDCA because "a common law right of action exists." *Hr'g on S. 1944 Before a Subcomm. of the Comm. on Commerce of the U.S. Senate*, 73d Cong. 2d Sess. 400, 403 (1933). And in the 1962 amendments, which substantially expanded the FDA's powers under the Act, Congress included a savings clause: "Nothing in the amendments made by this Act . . . shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law." Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962). This approach stands in marked contrast to Congress's regulation of medical devices, which includes an express preemption provision that "no State ... may establish or continue in effect with respect to a device intended for human use any requirement - (1) which is different from, or in addition to, any requirement applicable under this chapter to the device; and (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under this chapter." 21 U.S.C. § 360k(a).

Congress amended the FDCA again in 2007 with the Food & Drug Administration Amendments Act of 2007 (FDAAA), and it again chose not to enact a generally applicable express preemption provision, despite efforts by the pharmaceutical industry to ob-

tain such a provision.[2] The legislative record indicates that Congress considered the amendments' preemption implications[3] and that, ultimately, Congress decided to expressly preempt only a very narrow category of state regulation. *See* Pub. L. 110-85, Title VIII, § 282(d), 121 Stat. 922 (Sept. 27, 2007) (preempting state registering requirements for certain clinical trials).[4] And Congress rejected a provision in the Senate bill that would have required FDA approval of all label changes, instead "adopt[ing] a rule of construction to make it clear that manufacturers remain responsible for updating their labels." *Wyeth*, 555 U.S. at 568 (citing 121 Stat. 925-26); *see*

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[2] *See* Pub. L. No. 110-85, 121 Stat. 823 (2007); David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 96 Geo. L.J. 461, 468 & n.27 (2008) (noting the disappointment of counsel for the pharmaceutical industry).

[3] *See* 153 Cong. Rec. S11832, col. 3, S11833, cols. 1-2 (daily ed. Sept. 20, 2007) (Sen. Kennedy); *id.* at S11834, cols. 2-3 (Sen. Leahy); *id.* at S11835, col. 3 (Sen. Durbin).

[4] Petitioner's *amici* have argued that the 2007 FDAAA "modifies] the preemption equation presented in *Levine*." Br. of *Amici Curiae* Pharmaceutical Research and Manufacturers of America and Biotechnology Innovation Organization in Support of Petitioner in No. 17-290, *Merck Sharp & Dohme Corp. v. Albrecht* at 4 (Sept. 2018). This is an odd assertion, given that this Court's opinion in *Wyeth* explicitly considered the impact of the FDAAA. For the Court, the most salient aspect of the 2007 amendment was its rejection of a provision in the Senate bill to require FDA preapproval for all label changes. *See* 555 U.S. at 567-68. Neither this Court nor the United States, which briefed the impact of the FDAAA in *Wyeth*, suggested that the FDAAA broadened the FDCA's preemptive effect. *See* Br. for the United States as *Amicus Curiae* Supporting Petitioner in No. 06-1249, *Wyeth v. Levine*, at 32-33 (June 2008) (stressing only that "those amendments do not reflect any intent to *limit* the FDCA's preemptive effect") (emphasis added).

21 U.S.C. § 355(o)(4)(I). There would be little point to preserving the manufacturer's responsibility regardless of FDA action if the FDA had sole responsibility to determine the label's content. Rather, Congress plainly intended that other actors—in particular, courts adjudicating state tort claims—would also have a role in identifying inadequate warnings.

Nor has Congress granted the FDA authority to unilaterally alter the preemptive effect of its drug labeling regulation. The Medical Devices Act expressly preempts "different" or "addition[al]" state law requirements and delegates to the FDA a specific role in determining the Act's preemptive reach, but nothing in the FDCA indicates that Congress intended FDA drug labeling regulation to have equivalent effect. Nor is there any provision conferring authority on FDA to make a determination as to when consistent but different or additional state requirements would be preempted. *Compare* 21 U.S.C. § 360k, *with* 21 U.S.C. § 301, *et seq.*; *see also Medtronic, Inc. v. Lohr*, 518 U.S. 470, 495-496 (1996) (discussing the FDA's unique role in determining the scope of § 360k's pre-emptive effect).

This Court's decision in *Wyeth* noted all this statutory history when it held that Congress did not intend to broadly preempt state law claims against manufacturers of name-brand drugs. 555 U.S. at 573-81. Justice Stevens's majority opinion explained that "through many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain ad-

equate as long as the drug is on the market." *Id.* at 570-71. This emphasis on the manufacturer's responsibility underscores that "Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness." *Id.* at 575. The Court noted that "[f]ailure-to-warn actions, in particular, lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times." 555 U.S. at 579. *Wyeth* thus concluded that Congress failed to provide any federal remedy for consumers under the FDCA precisely because "it determined that widely available state rights of action provided appropriate relief for injured consumers." *Id.* at 574.

Wyeth emphasized that "'[t]he case for federal pre-emption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to stand by both concepts and to tolerate whatever tension there [is] between them.'" 555 U.S. at 575 (quoting *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166–167 (1989). This Court thus construed the text and history of the FDCA as fundamentally preservative of state law claims. As a statutory holding that Congress may revisit if it is so inclined, *Wyeth*'s reading of the FDCA is entitled to a *stare decisis* presumption of "enhanced force." *Kimble*, 135 S. Ct. at 2409. Whatever the impact of *Rice*'s broader presumption against preemption in this case, *Wyeth*'s settled reading of the FDCA imposes a heavy burden on Petitioner to establish preemption. And to the extent that Petitioner's arguments would tend to undermine the role for state law that Congress sought to preserve, those arguments should be rejected.

II. The Preemption Inquiry in this Case Should Focus on Whether Merck Could Legally Have Changed Its Label to Comply with State Law.

This Court has repeatedly said that "'[t]he purpose of Congress is the ultimate touchstone' in every pre-emption case." *Medtronic*, 518 U.S. at 485 (quoting *Retail Clerks v. Schermerhorn*, 375 U.S. 96, 103 (1963). As just discussed, *Wyeth* held that Congress generally intended to preserve state tort law when it enacted the FDCA's regulatory regime for brand-name drugs. And this Court's decision in *PLIVA*, 564 U.S. at 618, makes clear that Congress intended state law to give way only where federal law makes it illegal for a drug manufacturer to unilaterally alter its label in order to comply with a state-law duty. The preemption question in this case thus reduces to whether Merck could have added a warning about atypical femoral fractures to its label without further action by the FDA.

However, the parties to this case (and the court of appeals) have focused on a subtly but importantly different question. Petitioners have drawn Respondents into a vigorous debate over the meaning of the FDA's "complete response letter" rejecting Merck's proposed change to the Fosamax label, and what that letter signifies about how the agency might have responded if Merck had proposed a label change focused—as Respondents argue state law required—on atypical femoral fractures. *Amici* suggest that this focus mistakes the nature of the preemption inquiry.

Because the purpose of Congress is the "ultimate touchstone" for preemption, the question is whether *Congress*—not the agency—intended to displace state law under the circumstances of this case. This could have happened in only three ways:

1) Congress could have intended to preempt any state-law based changes that departed from the FDA-approved label;

2) Congress could have delegated the authority to preempt particular state law duties to the FDA;

3) Congress could have delegated to the FDA the authority to take particular substantive actions with regard to a manufacturer's label that might create a conflict with a state-law duty to warn.

The first of these possibilities describes Congress's regime for *generic* drugs that this Court held to have preemptive effect in *PLIVA*, but *Wyeth* rejected arguments that the name-brand regime had similar effect. 555 U.S. at 568-71. The second describes the FDCA regime for medical devices, which *Wyeth* contrasted with the name-brand drug regime. *Id.* at 567. The third certainly *does* describe the name-brand drug regime, at least insofar as manufacturer that unilaterally changed its label through the CBE process in response to a state-law duty could not continue to use that label if the FDA rescinded it. *Id.* at 571.

There is no such FDA action here, however. This case concerns whether a quite different agency action—the denial of Merck's voluntary PAS application for pre-clearance of a particular label—also effectively preempts a state-law duty to warn. One

might argue for that result on two distinct grounds: first, that the denial *itself* made it illegal for Merck to adopt the warnings state law required; or second, that the denial indicated the FDA's intent to reject the state-law-required label in the future if Merck were to adopt it through the CBE process.

Amici submit that neither of these theories is viable. We think it is unlikely that Congress intended for PAS denials to foreclose resort to the CBE process, much less to be independently preemptive of state law. And it is even less likely that Congress would have wanted courts to speculate about the import of PAS denials for future decisions that the FDA might make. In assessing these arguments, moreover, this Court should be mindful that both theories would undermine Congress's concern for preserving the role of state law in drug safety regulation and shift key decisions about preemption to the FDA. As we discuss below, shifting preemptive authority to administrative agencies undermines key aspects of our federal structure.

A. This Court should avoid shifting the focus of the preemption inquiry from Congress's intent to that of the agency.

The opening line of the United States' brief states that "[t]his case concerns the circumstances under which a decision of the [FDA] rejecting proposed changes to the labeling of a brand-name drug preempts state-law tort claims that allege that the drug manufacturer failed to provide adequate warnings on its labeling." United States Brief at 1. This characterization suggests a shift in focus from Con-

gress's intent to the agency's action. To be sure, agency action can, in appropriate cases, preempt state law. But that effect is cabined in at least three ways. First, "[t]he Supremacy Clause . . . requires that pre-emptive effect be given only to those federal standards and policies that are set forth in, or necessarily follow from, the statutory text that was produced through the constitutionally required bicameral and presentment procedures." *Wyeth*, 555 U.S. at 586 (Thomas, J., concurring in the judgment).[5] Second, only agency action "with the force of law" can preempt state law. *See Wyeth*, 555 U.S. at 576, 580.[6] And third, this Court owes no special deference to an agency's conclusion that state law is preempted. These principles derive from structural concerns that federal agency processes—in contrast to Congress's lawmaking procedures—incorporate no protections whatsoever for state regulatory autonomy.[7]

Federal agencies do not represent the states, and their interests do not always align. *See*,

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[5] See also Stuart M. Benjamin & Ernest A. Young, Tennis with the Net Down: Administrative Federalism without Congress, 57 Duke L. J. 2111, 2133-35 (2008) (insisting that the status of agency action as supreme federal law derives from Congress's action).

[6] *See also Arizona v. United States*, 567 U.S. 387, 445 (2012) (Alito, J., concurring in part and dissenting in part) (describing as "remarkable" the claim that "a state law may be pre-empted, not because it conflicts with a federal statute or regulation, but because it is inconsistent with a federal agency's current enforcement priorities . . . [which] are not law"); David S. Rubenstein, *The Paradox of Administrative Preemption*, 38 Harv. J. L. & Pub. Pol'y 267 (2015).

[7] *See generally* Ernest A. Young, *Executive Preemption*, 102 Nw. U. L. Rev. 869, 871-81 (2008).

e.g. Letter from Steven Rauschenberger, president, National Conf. of State Legis. to Michael Leavitt, secretary of HHS (Jan. 13, 2006) (complaining that the FDA's preemption preamble at issue in *Wyeth* showed a "complete disregard for our dual system of government"). Indeed, agencies are notoriously unwilling to consider federalism values even where standing executive orders require them to do so. *See* Nina A. Mendelson, *Chevron and Preemption*, 102 Mich. L. Rev. 737, 783 (2004) ("In 1999, the General Accounting Office reported that only five federalism impact statements had been prepared for the over 11,000 final rules agencies issued between April 1996 and December 1998."). Administrative action likewise evades not only the political but also the *procedural* safeguards of federalism. To the extent that Article I's lawmaking gauntlet tends to preserve state autonomy, federal agency action threatens federalism by circumventing that procedure. *See* Bradford R. Clark, *The Separation Powers as a Safeguard of Federalism*, 79 Tex. L. Rev. 1321, 1433 (2001); Young, *Executive Preemption*, *supra* note 7, at 876-77.

It is true, of course, that agency expertise will be valuable with respect to certain aspects of the preemption decision. But agencies have little comparative advantage with respect to the basic task of statutory construction. Preemption determinations require interpretations of both federal and state law, moreover, and federal agencies have no expertise with respect to the latter. *See* Thomas W. Merrill, *Preemption and Institutional Choice*, 102 Nw. U. L. Rev. 727, 758 (2008). Here, for example, the FDA has no particular expertise to assess what warnings state law might require. Deference to agency

preemption determinations, moreover, allows agencies to expand their own power through preemption. *See* Merrill, *Preemption*, *supra*, at 756; William W. Buzbee, *Asymmetrical Regulation: Risk, Preemption, and the Floor/Ceiling Distinction*, 82 N.Y.U. L. Rev. 1574, 1590 (2007) (identifying agencies' incentive to make themselves the sole locus of regulatory choice).

This Court has been wary of according independent preemptive effect to agency actions and of deferring to an agency's determination of the preemptive effects of its regulations or governing statutes. In *Wyeth*, this Court emphasized that "Congress has not authorized the FDA to pre-empt state law directly," and it refused to defer to the FDA's opinion that state failure to warn claims were preempted. 555 U.S. at 576-81. Likewise, Justice Thomas's majority opinion in *PLIVA* rejected the suggestion that courts should "defer to an agency's ultimate conclusion about whether state law should be pre-empted." 564 U.S. at 613 n.3.

As discussed above, *Wyeth* held that Congress intended broadly to preserve state law governing drug warnings; hence, this Court restricted preemption to cases of impossibility and construed that category narrowly. *See* 555 U.S. at 570-73, 574-76. The key question in an impossibility case is whether it was "lawful under federal law for the Manufacturers to do what state law required of them." *PLIVA*, 564 U.S. at 618. As Professor Nelson puts it, "preemption occurs if and only if state law contradicts a valid rule established by federal law." Caleb Nelson, *Preemption*, 86 Va. L. Rev. 225, 231 (2000). *PLIVA*—which involved failure to warn claims against generic

drugmakers that must replicate the brand-name version's warning label—thus stressed that "[i]f the Manufacturers had independently changed their labels to satisfy their state-law duty, they would have violated federal law." *PLIVA*, 564 U.S. at 618. In this case, the FDA's complete response letter does not establish impossibility under this standard.

B. The FDA's complete response letter did not render it illegal for Merck to comply with state law duties to strengthen its label.

Neither Petitioner nor the United States makes a serious argument that the FDA's denial of Merck's PAS application independently made it illegal for Merck to change its label unilaterally in order to satisfy its state-law duty to warn. Petitioner does assert that "[b]ecause of that rejection, it was impossible for Merck to revise its label to conform to the state-law duties that respondents allege, without violating federal law in the process." Petitioner's Brief at 35. But that assertion neither cites any statutory or regulatory provision nor articulates how the PAS and CBE procedures interact within the regulatory scheme. The structure of that scheme makes clear, however, that a PAS denial cannot itself have preemptive effect.

First, the PAS procedure is an alternative to the CBE procedure permitting a manufacturer to unilaterally change its label in response to safety concerns. Neither Petitioner nor its *amici* have pointed to any statutory or regulatory provision indicating that rejection of a PAS application would fore-

close resort to the CBE procedure.[8] Reading a PAS application to forestall resort to the CBE process, moreover, would run counter to the FDCA's general intent to preserve the role of state tort remedies.

Second, Merck never pursued the PAS process to a final conclusion. A complete response letter "informs sponsors of changes that must be made before an application can be approved, with no implication as to the ultimate approvability of the application." 73 Fed. Reg. 39,588 (2008). An applicant receiving such a letter has three options: (1) "[r]esubmit the application . . . , addressing all deficiencies identified in the complete response letter"; (2) [w]ithdraw the application"; or (3) request a hearing at which FDA will make a final determination whether to approve or reject the application. 32 C.F.R. § 314.110(b). The agency's communication to Merck thus plainly contemplated further action of various kinds. It was "of a merely tentative or interlocutory nature," rather than "the consummation of the agency's decisionmak-

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[8] Construing a PAS rejection to operate in this way would be inconsistent with statute's handling of a similar situation, in which the Secretary of Health and Human Services may request changes to a label based on new safety information. *See* 21 U.S.C. § 355(o)(4). Such a request by the Secretary initiates an iterative process that may ultimately result in a coercive order. Critically, however, this section has a "[r]ule of construction" that this Court has construed to underscore the ultimate responsibility of the manufacturer for the adequacy of the label. *See* § 355(o)(4)(I); *Wyeth*, 555 U.S. at 567-68. This rule strongly suggests that the manufacturer remains subject to state tort duties notwithstanding the Secretary's initiation of a process to change the label.

ing process." *Bennett v. Spear*, 520 U.S. 154, 156, 178 (1997).[9]

Because it is not final and therefore not subject to judicial review, and because it has a relatively low degree of formality, the FDA's complete response letter is not agency action with the force of law. The agency's letter thus cannot preempt state law on its own. Nor can it render manufacturer action impossible. Even if a final agency order resolving the PAS process might have preemptive effect, Merck never took the process that far. Until the agency takes action with the force of law foreclosing the label changes that state law requires, there can be no impossibility preemption.

Finally, the FDA rejected Merck's PAS application for a label change that was quite different from the one that Respondents allege state law requires. It makes no sense to assume that because the FDA did not approve a particular change that would have added warnings to Fosamax's label, the agency would have rejected *any* change to that label warning—even one warning of a distinct risk. *See* Michael M. Gallagher, *Clear Evidence of Impossibility Preemption after* Wyeth v. Levine, 51 Gonzaga L. Rev. 439, 466-67 (2016) ("If the FDA neither considered nor rejected the precise warning sought by the plaintiff, then the failure to warn claim is not preempted."). Even if the PAS denial were final

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[9] *Cf. Holistic Candlers and Consumers Ass'n v. FDA*, 664 F.3d 940, 944-45 (D.C. Cir. 2012) ("[L]ike other agency advice letters that we have reviewed over the years, FDA warning letters do not represent final agency action subject to judicial review.").

agency action with the force of law, that action answered a question that Respondents have not asked.

C. The complete response letter cannot establish preemption by providing evidence of what the FDA *would have done* had Merck changed its label to meet state law requirements.

Petitioner's primary argument seems to be not that the complete response letter preempted state law in itself but rather that it signaled what would have happened if Merck had tried to adopt a label warning of atypical femoral fractures unilaterally through the CBE procedure. This argument likewise cannot establish preemption.

The first problem with this way of framing the question is that it contravenes *PLIVA*. That decision firmly resisted the notion that probabilistic judgments about what the FDA *might* have done should govern the preemption analysis. In that case, the plaintiffs argued that although federal law forbade a generic drug manufacturer from unilaterally changing its label, the manufacturer could have notified FDA of the danger and sought changes both for the brand-name and the generic label. But the possibility that FDA might ultimately have mandated such a change was insufficient to avoid preemption. *See PLIVA*, 564 U.S. at 619-21. *PLIVA* thus rejected the notion that "conflict pre-emption must take into account hypothetical federal action." *Id.* at 621. "The question for 'impossibility'," this Court insisted, "is whether the private party could *independently* do

under federal law what state law requires of it." *Id.* at 620 (emphasis added).

The second set of difficulties are practical. Much of the debate between the parties and their other *amici* concerns whether the complete response letter's preemptive effect raises a question of law, to be decided by the court, or a question of fact that must go to the jury. If the preemption question is a probabilistic one about what the FDA might do, based not only on complete response letters but also any other available evidence of the agency's intent, then the Third Circuit's conclusion that this is a jury question makes some sense. But surely that is a reason to change the question—not simply to take it from the jury. Preemption is ordinarily a legal question for the court precisely because it focuses on conventional interpretation of congressional intent, not on an effort to assess the future intentions of agency officials.

Treating Petitioner's probabilistic counterfactual as determinative would have other adverse consequences. If validity of preemption defenses in drug cases comes to turn on what the FDA would do in various circumstances that it has not already ruled upon, then parties to state tort litigation will have strong incentives to seek discovery from the FDA concerning its internal deliberations. It should not create incentives to burden the agency with inquiries into the agency's decisionmaking process in an effort to divine how the agency might respond to a question not put to it.

To be sure, *Wyeth* suggested that clear evidence that the FDA would not have approved a

change to [a drug's] label" could establish impossibility. 555 U.S. at 571. But the Court telegraphed what such a showing would require in the very next paragraph, stating that "Wyeth . . . does not argue that it attempted to give the kind of warning required by the Vermont jury but was prohibited from doing so by the FDA." *Id.* at 572. This strongly suggests that a manufacturer must adopt the warning required by state law pursuant to the CBE procedure and then have the FDA actually reject that order through final action with the force of law. This is the only standard consistent with *PLIVA*'s insistence that the preemption inquiry may not "take into account hypothetical federal action." 564 U.S. at 621.

This Court should hesitate before extending *Wyeth*'s proviso any further. The suggestion that a drug manufacturer need not adopt a state-required warning because the FDA would likely reject it is similar in structure to futility-based exceptions to rules requiring litigants to pursue certain remedies or limiting the grounds upon which a court can act. When such exceptions are allowed, they tend to be very narrow. A party cannot challenge a state or local government's taking of property, for example, until the government has definitively rejected the proposed property use, and it must pursue available procedures to obtain such a ruling unless such an action would be futile. *See, e.g., Palazzollo v. Rhode Island*, 533 U.S. 606, 624-26 (2001). But the relevant state governmental entity must have taken a definitive position that leaves no doubt as to the incursion on the plaintiff's property rights. *See id.*[10] Similarly,

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[10] *See also MacDonald, Sommer & Frates v. Yolo Cty.*, 477 U.S. 340, 348 (1986) ("[A]n essential prerequisite to [a regulato-

a reviewing court may generally uphold administrative agency action only on the grounds upon which the agency relied. *SEC v. Chenery Corp.*, 318 U.S. 80 (1943). A court may avoid a remand only if "[t]here is not the slightest uncertainty as to the outcome of a proceeding before the [agency]," and thus "[i]t would be meaningless to remand." *NLRB v. Wyman-Gordon Co.*, 394 U.S. 759, 766 n.6 (1969).[11]

In the context of collateral review of state criminal convictions by federal *habeas corpus*, by contrast, there generally is *no* such futility exception. Rather, failure to present an argument to the state courts is a procedural default barring federal *habeas* review, even if state precedent suggests the argument would likely be rejected. *See, e.g., Engel v. Isaac*, 456 U.S. 107, 130 (1982). The reason is that "[e]ven a state court that has previously rejected a constitutional argument may decide, upon reflection, that the contention is valid." *Id.*

These examples suggest that *Wyeth*'s dictum should be construed to absolve drug manufacturers from seeking to modify their labels as required by state law only in very narrow circumstances—if at all. As in the takings cases, manufacturers should have to show that the agency has taken final and definitive action concerning the required warnings (and not some other warning that might or might not be

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ry takings claim] is a final and authoritative determination of the type and intensity of development legally permitted on the subject property.").

[11] *See also INS v. Orlando Ventura*, 572 U.S. 12, 17 (2002) (recognizing an exception to the remand requirement only in very rare circumstances).

similar). But there is also much to be said for affording the FDA—like the state courts in the *habeas* context—an opportunity to reconsider by provisionally adopting the state-required label through the CBE process even if a PAS denial were directly on point.

III. The Presumption Against Preemption Applies in this Case.

For over seventy years, this Court has begun its preemption inquiries "with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Rice*, 331 U.S. at 230. Petitioner's *amici* seek to use this case as a vehicle for a general assault on the *Rice* presumption and its application in implied preemption cases—both arguments that this Court has rejected before.[12] For the reasons we explore below, this Court should reject them again.

A. The *Rice* presumption is well-established and consistent with the text of the Supremacy Clause.

Although it may not be necessary to decide this case, given *Wyeth*'s interpretation of this particular statutory regime, the *Rice* presumption against preemption remains 'cornerstone[] of [this Court's] pre-emption jurisprudence." *Wyeth*, 555 U.S. at 565 (citing *Medtronic*, 518 U.S. at 485). That is true not-

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[12] *See generally* Ernest A. Young, *'The Ordinary Diet of the Law': The Presumption Against Preemption in the Roberts Court*, 2011 Sup. Ct. Rev. 253, 276-78 (2012) (discussing the Court's rejection of prior attacks on the presumption against preemption).

withstanding the assertion of Petitioner's *amici* that "[n]o basis exists in the Constitution for applying a presumption against preemption—in this or any other case." Brief of Washington Legal Foundation as *Amicus Curiae* in Support of Petitioner in No. 17-290, *Merck Sharp & Dohme Corp. v. Albrecht*, at 18 (Sept. 20, 2018). Pro-preemption *amici* have been making that argument for decades, and this Court has never adopted it.

The reason for that is that the presumption against preemption plays a central role in modern federalism jurisprudence. *See generally* Young, *supra* note 12, at 257-83 . This Court's Commerce Clause cases leave most areas of regulatory concern subject to concurrent national and state authority, with the result that the most critical federalism questions concern not so much what Congress can do, as a matter constitutional power, but what it has done—and how much room it has left for state regulation. *Compare, e.g.*, *Gonzales v. Raich*, 545 U.S. 1 (2005) (construing Congress's commerce power broadly to reach homegrown medical marijuana), *with Gonzales v. Oregon*, 546 U.S. 243 (2006) (construing the Controlled Substances Act not to authorize the Attorney General to preempt Oregon's Death with Dignity Act). Historically speaking, the *Rice* presumption against preemption developed as a response to the expansion of Congress's commerce power during the New Deal period: as the scope of Congress's action expanded, it was essential to ensure that federal activity did not disable large swaths of state regulation without clear evidence that Congress intended to do so. *See* Stephen A.

Gardbaum, *The Nature of Preemption*, 79 Cornell L. Rev. 767, 806-07 (1994).[13]

Moreover, the *Rice* presumption fits well with this Court's recognition that structural and political safeguards play a critical role in protecting state autonomy against federal encroachments. *See Garcia v. San Antonio Metro. Trans. Auth.*, 469 U.S. 528, 550-54 (1985). In *Gregory v. Ashcroft*, 501 U.S. 452 (1992), this Court explained:

> [I]nasmuch as this Court in *Garcia* has left primarily to the political process the protection of the States against intrusive exercises of Congress' Commerce Clause powers, we must be absolutely certain that Congress intended such an exercise. "[T]o give the state-displacing weight of federal law to mere congressional *ambiguity* would evade the very procedure for lawmaking on which *Garcia* relied to protect states' interests."

Id. at 464 (quoting Laurence Tribe, *American Constitutional Law*, § 6-25, at 480 (2d ed. 1988)); *see also*

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[13] Petitioner's *amici* are simply incorrect to claim that the *Rice* presumption does not "enjoy a long pedigree." Washington Legal Foundation Br., *supra*, at 20. The doctrine arose in the 1930s and 1940s, at the same time that this Court accepted a considerably broader notion of Congress's regulatory powers. *See Rice*, 331 U.S. at 229-36; *Mintz v. Baldwin*, 289 U.S. 346, 350-52 (1933) (both articulating a presumption against preemption); *Wickard v. Filburn*, 317 U.S. 111 (1942); *NLRB v. Jones & Laughlin Steel Corp.*, 301 U.S. 1 (1937) (both adopting a more expansive view of Congress's regulatory authority). *See generally* Gardbaum, *supra*, at 805-07.

Murphy v. NCAA, 138 S. Ct. 1461, 1477 (2018) (emphasizing the importance of political checks on federal action). Requiring clear evidence of Congress's intent to alter the federal balance—whether by regulating the qualifications of state officers, as in *Gregory*, or by displacing state law through preemption—is important in two respects. It provides a political check, by providing notice to the States' representatives in Congress, and a procedural check, by requiring that state-displacing choices overcome the Constitution's built-in hurdles to federal legislative action.[14]

As *Gregory* illustrates, the *Rice* presumption is one of many rules of construction that protect state autonomy. *See, e.g., Arlington Cent. Sch. Dist. Bd. of Educ. v. Murphy*, 548 U.S. 291, 296 (2006) (requiring that Congress clearly state conditions on grants of federal funds to the States); *Jones v. U.S.*, 529 U.S. 848, 858 (2000) (requiring a clear statement of Congress's intent to regulate at the outer limits of its Commerce Clause authority); *Will v. Mich. Dep't of State Police*, 491 U.S. 58, 65 (1989) (requiring a clear statement of Congress's intent to subject states to liability under federal statutes).[15] Because preemption questions arise so frequently, however, the *Rice* presumption is the most important of these rules.

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[14] *See generally* Young, *Ordinary Diet*, *supra* note 12, at 265; Clark, *supra*, 1330.

[15] *See generally United States v. Bond*, 572 U.S. 844, 857-58 (2014) (stressing the importance of these rules, including the *Rice* presumption); Thomas W. Merrill, *Rescuing Federalism After* Raich: *The Case for Clear Statement Rules*, 9 Lewis & Clark L. Rev. 823 (2005).

Petitioner's *amici* contend that a presumption against preemption is contrary to the original understanding of the Supremacy Clause, *see* Washington Legal Foundation Br., *supra*, at 18-19 (citing Caleb Nelson, *Preemption*, 86 Va. L. Rev. 225, 304 (2000). Other *amici* made the same argument in *Wyeth*,[16] and we discussed it at some length in our *amicus* brief in that case.[17] The short answer is that Professor Nelson's originalist argument objects only to an anti-preemption rule of construction considerably stronger than anything this Court has applied under *Rice*. *See* Nelson, *supra*, at 293-94 (stating that "[o]ne should not take [his] point too far" and that he has no objection to the notion that "judges should generally be reluctant to infer pre-emption."); Young, *Ordinary Diet*, *supra* note 12, at 311-15 (elaborating this point). In any event, this Court has necessarily rejected any argument that *Rice* is unconstitutional by continuing to apply the presumption.

B. *Rice*'s presumption against preemption applies in implied conflict cases.

Petitioner's *amici* also make a narrower argument that, even if *Rice* is good law, it should not apply in *implied* preemption cases. The *amici* supporting the petitioner in *Wyeth* made this precise argu-

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[16] *See* Br. of the Chamber of Commerce of the United States of America as *Amicus Curiae* in Support of Petitioner in No. 06-1249, *Wyeth v. Levine*, at 18 (June 2008).

[17] *See* Br. of *Amicus Curiae* Constitutional and Administrative Law Scholars in Support of Respondent in No. 06-1249, *Wyeth v. Levine*, at 9-14; *see also* Young, *Ordinary Diet*, *supra*, at 310-24 (discussing Professor Nelson's argument).

ment in that case,[18] but this Court explicitly rejected it, observing that "this Court has long held to the contrary." 555 U.S. at 565 n.3 (citing *California v. ARC America Corp.*, 490 U.S. 93, 101-102 (1989); *Hillsborough Cty. v. Automated Medical Labs., Inc.*, 471 U.S. 707, 716 (1985); and *Rush Prudential HMO, Inc. v. Moran*, 536 U.S. 355, 387 (2002)).[19] The cases that Petitioners' amici cite as "openly question[ing] whether the presumption should ever apply in conflict-preemption cases," Washington Legal Foundation Br., *supra*, at 21, say no such thing. Rather, those cases—*Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 374 n.8 (2000), and *United States v. Locke*, 529 U.S. 89, 108 (2000)—both involved foreign affairs considerations raising questions whether the ordinary *Rice* presumption should apply in that context.[20]

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[18] *See* Chamber of Commerce Br. in *Wyeth*, *supra*, at 27 ("[T]he Court should take this opportunity to make clear that the presumption against preemption – whatever its applicability to questions of field preemption – is simply inapplicable to cases involving conflict preemption.").

[19] *See also, e.g., Pharm. Research and Mfrs. of America v. Walsh*, 538 U.S. 644, 666 (2003) (plurality opinion) (applying the *Rice* presumption to a conflict claim under the Medicaid statute); *accord id.* at 681 n.4, 682 (Thomas, J., concurring in the judgment) (same); *Bldg. & Constr. Trades Council v. Associated Builders & Contractors of Mass./R. of the Metropolitan Dist. I., Inc.*, 507 U.S. 218, 224 (1993) (applying *Rice* presumption to conflict preemption under the NLRA); *Ca. Fed. Sav. & Loan Ass'n v. Guerra*, 479 U.S. 272, 281, 288 (1987)) (applying a presumption against preemption in the course of rejecting a claim that a state pregnancy discrimination statute conflicted with Title VII).

[20] *See also* Jack Goldsmith, *Statutory Foreign Affairs Preemption*, 2000 Sup. Ct. Rev. 175 (2001) (considering whether

Whatever the merits of the position that *Rice* should not apply (or should apply differently) in *express* preemption cases, we think the case for a presumption against preemption is particularly strong where Congress has not articulated its preemptive intent in statutory text.[21] And the same analysis of

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different presumptions should govern preemption in foreign and domestic cases). Petitioner's *amici* also stress that, of five preemption cases during the 2011, "*none* discussed the presumption against preemption." Washington Legal Foundation Br. at 24. Although no majority opinion invoked *Rice* explicitly that term, *Whiting* stated that "[o]ur precedents 'establish that a high threshold must be met if a state law is to be pre-empted for conflicting with the purposes of a federal Act.'" *Chamber of Commerce v. Whiting*, 563 U.S. 582, 607 (2011) (quoting *Gade v. National Solid Wastes Mgt. Assn.*, 505 U.S. 88, 110 (1992) (Kennedy, J., concurring in part and in the judgment)). And taken altogether, the 2011 term cases "provide some evidence that the Court is raising the overall bar for conflict preemption"—not lowering it. Young, *Ordinary Diet*, *supra* note 12, at 328.

[21] One of Petitioner's *amici* asserts that "[t]his Court has recently abolished any 'presumption against preemption' in express-preemption cases." Washington Legal Foundation Br., *supra*, at 21 (quoting *Puerto Rico v. Franklin California Tax-Free Trust*, 136 S. Ct. 1938, 1946 (2016)). But that oversimplifies the situation dramatically. *Franklin* did state that "because the statute 'contains an express pre-emption clause,' we do not invoke any presumption against pre-emption but instead 'focus on the plain wording of the clause, which necessarily contains the best evidence of Congress' pre-emptive intent." 136 S. Ct. at 1946 (quoting *Whiting*, 563 U.S. at 594). But the presumption against preemption *never* applies when statutory language is clear. That is probably why *Franklin* did not discuss—and certainly did not overrule—decisions like *Altria Group, Inc. v. Good*, 555 U.S. 70 (2008), which stated that "when the text of a pre-emption clause is susceptible of more than one plausible reading, courts ordinarily 'accept the reading that disfavors pre-emption.'" *Id.* at 77 (quoting *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005)). As *Bates* explained, concluding that a

the Supremacy Clause's original understanding that Petitioner's *amici* rely upon to challenge the *Rice* presumption generally also concludes that *conflict* preemption should be construed far more narrowly than under current law.[22] And although conflict preemption cases lack an express preemptive text to which to apply a rule of statutory construction, they typically do involve two kinds of ambiguity: First, the substantive content of federal law may be ambiguous, so that it is unclear whether that law actually creates a conflict with state law. In such cases, the presumption suggests courts should interpret federal

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statute expressly preempts some aspects of state law "says nothing about the *scope* of that pre-emption." 544 U.S. at 443-44 (emphasis in original).

Franklin's statement on express preemption clauses quoted *Whiting*, 563 U.S. at 594, and cited *Gobeille v. Liberty Mut. Ins. Co.*, 136 S. Ct. 936, 946 (2016). But neither case purported to revisit *Altria* or *Bates*, and neither supports categorically excluding *Rice*'s presumption where there is an express preemption clause. *Whiting*, like *Franklin*, found the language of the federal statute clear and had no occasion to resort to canons of construction. The Court may also have wished to avoid deciding whether *Rice* applies to laws governing immigration—an area of exceptionally broad federal authority. *Gobeille* held simply that the presumption against preemption was overcome by state law's "direct regulation of a fundamental ERISA function," while acknowledging that *Rice* does control in many instances under ERISA. 136 S. Ct. at 946 (citing *De Buono v. NYS-ILA Medical and Clinical Services Fund*, 520 U.S. 806 (1997) (applying *Rice* in an ERISA case notwithstanding ERISA's express preemption clause)).

[22] *See* Nelson, *supra*, at 260 (arguing that state law should be preempted only if there is a "logical contradiction" between state and federal law); *see also Wyeth*, 555 U.S. at 590 (Thomas, J., concurring in the judgment) (adopting this part of Professor Nelson's analysis and concluding that it requires a narrower approach to conflict preemption).

law narrowly to avoid the conflict.[23] Second, a given conflict between federal and state law may be sufficiently minor that Congress would have preferred for state and federal law to operate side by side.[24] Here, the *Rice* presumption suggests simply that minor conflicts should be insufficient to displace to state law.[25] In either sort of case, the presumption provides a useful default rule that protects state regulatory autonomy without foreclosing federal action where Congress's intent is clear.

Petitioners' *amici* are right about this much: This Court has been inconsistent in its references to

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[23] *Cf. Bates*, 544 U.S. at 449 (stating, in an express preemption case, that in choosing between "plausible alternative reading[s]" of a federal statute, courts "have a duty to accept the reading that disfavors pre-emption").

[24] *See, e.g., Crosby*, 530 U.S. at 373 (observing that "[w]hat is a sufficient obstacle is a matter of judgment, to be informed by examining the federal statute as a whole and identifying its purpose and intended effects"); *Bonito Boats*, 489 U.S. at 167 (acknowledging that sometimes Congress intends "to tolerate whatever tension there [is] between" state and federal law).

[25] *See, e.g.*, Young, *Ordinary Diet*, *supra* note 12, at 274-76; Thomas W. Merrill, *Preemption*, *supra*, at 743 (observing that preemption cases assess not simply whether "federal law . . . is in tension with state law" but also "whether this tension is sufficiently severe to warrant the displacement of state law"). Even leading advocates of broad preemption acknowledge this point. *See* Alan Untereiner, *The Defense of Preemption: A View from the Trenches*, 84 Tulane L. Rev. 1257, 1260 (2010) (observing that in conflict preemption cases, "courts make judgments about whether the degree of tension between federal and state laws rises to the level of an impermissible conflict under the Supremacy Clause"). And Professor Nelson argues that Congress is unlikely to intend to preempt all state law conflicting in any way with a federal statutes, without regard to degree. *See* Nelson, *supra*, at 279-82.

the presumption against preemption.[26] That phenomenon should not surprise anyone, however. *Rice* has never been an overwhelming presumption, and thus preemption cases turn importantly on the text, structure, and purposes of specific federal statutes. In many cases, a majority of the Court may find that statute *clearly* preempts (or does not preempt) state law. Because canons of construction come into play only when statutes are ambiguous, there is no reasons to invoke or discuss *Rice* in such cases. It follows that failures to mention the presumption in particular cases are not necessarily evidence of desuetude. And of course this Court *does* continue to invoke the presumption.[27]

CONCLUSION

The holding of the United States Court of Appeals for the Third Circuit that Respondents' state-law failure to warn claims are not preempted should be affirmed.

Respectfully submitted,

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[26] *See* Young, *Ordinary Diet*, *supra* note 12, at 308-09 (discussing possible reasons for this).

[27] *See, e.g.*, *CTS Corp. v. Waldburger*, 134 S. Ct. 2175, 2188 (2014) (plurality opinion); *Bond*, 572 U.S. at 858.

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No. 17-290

IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,

Petitioner,

v.

DORIS ALBRECHT, et al.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Third Circuit

BRIEF OF WASHINGTON LEGAL FOUNDATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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QUESTION PRESENTED

Whether the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301, et seq., preempts a state-law failure-to-warn claim when the Food and Drug Administration has rejected the brand-name drug manufacturer's application, which included all relevant scientific data, to change its drug's label to warn about the very risk underlying the claim.

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INTEREST OF *AMICUS CURIAE*[*]

Washington Legal Foundation is a nonprofit, public-interest law firm and policy center with supporters in all 50 states. WLF promotes and defends free enterprise, individual rights, limited government, and the rule of law. Since its founding in 1977, WLF has appeared as *amicus curiae* in important preemption cases, urging the Court to ensure that federal law operates efficiently and uniformly—as Congress intended. *See, e.g., ONEOK, Inc. v. Learjet, Inc.*, 135 S. Ct. 1591 (2015); *Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472 (2013); *Wyeth v. Levine*, 555 U.S. 555 (2009).

WLF believes that individual freedom, the American economy, and public health all suffer when state law, including state tort law, interferes or conflicts with federal regulatory regimes, including the Federal Food, Drug, and Cosmetic Act (FDCA) 21 U.S.C. § 301, et seq. Conflicting federal and state duties are not merely inefficient; they make it impossible for regulated parties to comply with both state and federal law without incurring serious liability.

The Supremacy Clause prevents state law from imposing that Hobson's choice on anyone. But the decision below, by denying federal preemption in the face of clear impossibility, would render the Supremacy Clause a dead letter.

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[*] No party's counsel authored any part of this brief. No person or entity, other than WLF and its counsel, helped pay for the preparation or submission of this brief. All parties have consented to the filing of WLF's brief.

STATEMENT OF THE CASE

In 1995, the FDA approved the prescription drug Fosamax for treating osteoporosis in older women. Pet. App. 5a, 12a. Over the next 15 years, published studies suggested a possible link between long-term Fosamax use and atypical femoral fractures. *Id.* at 13a-14a. Merck, Fosamax's manufacturer, alerted the FDA to these studies. *Id.* at 13a. In June 2008, the FDA asked Merck to submit all available information it had linking the use of bisphosphonates to femoral fractures. *Id.* at 14a. Merck complied fully. *Ibid.*

In September 2008, Merck submitted a prior-approval supplement (PAS) seeking the FDA's permission to revise portions of Fosamax's label. Pet. App. 14a-15a. Under the Adverse Reactions section, Merck proposed adding "low-energy femoral shaft fracture" as a potential adverse reaction. *Id.* at 16a. Under the Warnings & Precautions section, Merck proposed adding a new subsection entitled "Low-Energy Femoral Shaft Fracture," which warned that "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft"—the upper and middle thigh bone—"have been reported in a small number of bisphosphonate-treated patients." *Id.* at 15a-16a. The proposed warning added that "some" of those fractures were "stress fractures * * * occurring in the absence of trauma." *Ibid.*

In April 2009, an FDA liaison instructed Merck to "hold off" on changing the Warnings & Precautions label until the FDA could "decide on language" for a stronger precaution "if it is warranted." Pet. App. 17a-18a. Then, in May 2009,

the FDA issued its Complete Response Letter, *id.* at 18a, which reflected "FDA's complete review of the data submitted" and described "all of the specific deficiencies" the agency identified. *See* 21 C.F.R. 314. 110(a)(1), (2). While the FDA agreed that Merck could add "low-energy femoral shaft and subtrochanteric fractures" to the Adverse Reactions section of the label, it rejected Merck's proposed changes to the Warnings & Precautions section. Pet. App. 18a-19a.

The FDA determined that "[i]dentification of 'stress fractures' may not be clearly related" to the "fractures that have been reported in the literature." Pet. App 18a-19a. In the FDA's view, any "[d]iscussion of the risk factors for stress fractures [was] not warranted and [was] not adequately supported by the available literature and post-marketing adverse event reporting." *Ibid.* Following the FDA's response, Merck promptly updated the Adverse Reaction section of Fosamax's label.

The FDA issued a safety announcement in March 2010. It confirmed that the available data still had "not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures." Pet. App. 19a. In fact, no study had shown "even that Fosamax use was definitely associated with atypical fractures." *Id.* at 13a. So the FDA commissioned a task force to gather more information. *Ibid.*

In September 2010, the FDA's task force reported an "association" between atypical femoral fractures and long-term bisphosphonate use. Pet App. 121a. But the task force found nothing "proven

to be causal." *Ibid.* In response, the FDA announced that even though causation was "still not clear," the agency would begin "considering label revisions." *Id.* at 20a-21a.

In October 2010, the FDA directed bisphosphonate manufacturers to revise the Warnings & Precautions sections of their labels to disclose the risk of atypical femoral fractures. Pet. App. 21a. Even if such fractures were "potentially more closely related to" long-term use of bisphosphonates, the FDA still believed it was "not clear" whether bisphosphonates caused the fractures. *Ibid.* Nonetheless, upon obtaining clarification from the FDA, Merck added the FDA's approved language to the Warnings & Precautions section of Fosamax's label. *Id.* at 21a-23a.

After the FDA approved Fosamax's revised label, more than 1,200 Fosamax users who had allegedly suffered an atypical femoral fracture sued Merck for failing to warn of the risk of that injury. Pet. App. 23a. These lawsuits were combined in multi-district litigation (MDL) in the District of New Jersey. *Ibid.* Following a bellwether trial, the district court issued an opinion addressing Merck's impossibility-preemption defense. *Id.* at 25a.

Applying this Court's decision in *Wyeth v. Levine*, the district court found "clear evidence that the FDA would not have approved a change to the Precautions section of the Fosamax label" before the FDA's task force report. Pet. App. 168a. The district court then applied that preemption holding to all MDL cases in which the plaintiff's alleged injury occurred before September 14, 2010 (the date of the

FDA's task force report) and granted summary judgment to Merck in those cases. *Id.* at 152a.

The Third Circuit vacated and remanded. Pet. App. 1a-74a. The court announced that *Levine*, by requiring "clear evidence" that the FDA would refuse a label change before a state-law claim arising from that label will be preempted, imposed a burden of proof "synonymous with 'clear and convincing evidence.'" *Id.* at 37a. Under this heightened bar, a defendant must prove that it "is highly probable that the FDA would not have approved a change to the drug's label" to establish a preemption defense. *Ibid.*

According to the Third Circuit, that question—whether the FDA would have refused a label change—is strictly a question of fact for the jury. Pet. App. 38a-55a. "Because the [*Levine*] test requires the factfinder to speculate about hypothetical scenarios using inferences drawn from historical facts, reasonable jurors could reach a broad range of conclusions when confronted with this record." *Id.* at 67a-68a. The panel determined that "a reasonable jury applying a heightened standard of proof *could* conclude" that the FDA would have allowed the label change if Merck had worded it differently. *Id.* at 67a.

SUMMARY OF ARGUMENT

Under the Supremacy Clause, any conflicting state law must give way to federal law. This Court has recognized that complying with both federal and state law is "impossible" for drug manufacturers when "[i]t was not lawful under federal law for [them] to do what state law required of them."

PLIVA, Inc. v. Mensing, 564 U.S. 604, 618 (2011). This case is no exception.

The only way Merck could have avoided liability under New Jersey tort law would have been to strengthen Fosamax's label to warn of an increased risk of atypical femoral fractures. But Merck has shown decisively not merely that the FDA *would have* rejected a stronger Fosamax warning, but that the FDA *did* reject a stronger Fosamax warning. A "clearer" showing of impossibility preemption is hard to imagine.

True enough, under this Court's holding in *Wyeth v. Levine*, the FDA's mere approval of a brand-name label, standing alone, doesn't establish a federal ceiling for drug regulation. But *Levine* also makes clear that the FDA's formal rejection of a manufacturer's proposed shift to a stronger label does just that. Here, no one disputes that before the FDA's September 2010 task force report, federal law and New Jersey law imposed on Merck irreconcilable labeling duties. So under *Levine*'s reading of the Supremacy Clause, New Jersey's conflicting tort-law duty must give way to federal law.

But the Third Circuit disagrees. The panel below held that if a reasonable jury could find that the FDA would have approved a differently worded label than the one Merck proposed, the threshold legal question of preemption goes to the jury, not the court. In so holding, the appeals court invites a lay jury not only to second guess the FDA's labeling decision but also to speculate on a labeling decision the FDA *might* have made. That holding collides with this Court's preemption cases.

By focusing on what the FDA might have done rather than on what the FDA did, the decision below dilutes *Levine* beyond all recognition. As the United States has confirmed in its *amicus* brief, the FDA's rejection of Merck's proposed label turned solely on the available scientific data, not on Merck's choice of words. If the Court were to adopt the Third Circuit's view of conflict preemption on this record, it would render the Supremacy Clause "all but meaningless." *Bartlett*, 570 U.S. at 488. If, on the other hand, the Court does little more than apply *Levine* straightforwardly, the judgment below must be reversed.

Nor does any presumption against preemption apply here. In equating *Levine*'s "clear evidence" rule with a clear-and-convincing-evidence standard of proof, the panel below invoked the "presumption against preemption." Pet. App. 37a. But no basis exists in the Constitution for applying a presumption against preemption—in this or any other case. And nothing in logic supports such a presumption when, as here, preemption hinges on the existence of a genuine conflict between state and federal law. On the contrary, implied conflict preemption is the quintessential example of the Supremacy Clause at work.

ARGUMENT

I. RESPONDENTS' FAILURE-TO-WARN CLAIM IS PREEMPTED BECAUSE FEDERAL LAW PROHIBITED MERCK FROM PROVIDING A STRONGER WARNING.

Under the Supremacy Clause, state law that conflicts with federal law is "without effect." *Maryland v. Louisiana*, 451 U.S. 725, 746 (1981). Even without an express preemption provision in the federal law, state law is impliedly preempted if it is "impossible for a private party to comply with both state and federal requirements." *English v. Gen. Elec. Co.*, 496 U.S. 72, 79 (1990). That is this case. As shown below, because it was impossible for Merck to comply with New Jersey tort law without simultaneously violating federal law, any state-law liability premised on a failure to warn is fully preempted.

A. The Third Circuit's Holding Flouts This Court's Preemption Case Law.

1. The leading preemption precedent for brand-name drug manufacturers is *Wyeth v. Levine*. In *Levine*, a Vermont jury determined that Wyeth's "inadequate label" on its drug Phenergan failed to warn adequately "about the [gangrene] risks of IV-push administration" of that drug. 555 U.S. at 564. On appeal, Wyeth argued that the "FDA's approvals" of Phenergan's label provided it "with a complete defense to Levine's tort claims." *Id.* at 558-59.

The Court disagreed. While recognizing that "the FDA retains authority to reject labeling

changes," *Levine* emphasized that, under the FDCA, brand-name drug manufacturers are generally free to strengthen their drugs' labels when necessary. *Id.* at 571. The Court held that, "absent clear evidence that the FDA would not have approved a change to Phenergan's label," it could "not conclude that it was impossible for Wyeth to comply with both federal and state requirements." *Id.* at 572. Put another way, while the FDA's mere approval of a brand-name label does not, as Wyeth contended, establish a federal "ceiling for drug regulation," *id.* at 573, the FDA's denial of a manufacturer's requested label change would do precisely that.

Nor is that all. As this Court later clarified in *PLIVA v. Mensing*, a plaintiff's rank speculation about whether and how a drug manufacturer *might* have reconciled its federal and state-law duties is never enough to defeat preemption. In *Mensing*, the generic manufacturers argued that any state-law duty to strengthen their drug's label conflicts with their "ongoing federal duty of 'sameness,'" which requires a generic drug's label to "be the same as the [brand-name] drug product's labeling." 564 U.S. at 613. But the plaintiffs argued that the generic manufacturers' independent duty to alert the FDA to any newly discovered risks for their drugs made it "certainly possible" that the FDA would have approved a "safer label" had the manufacturers bothered to ask for one. *Id.* at 618-20.

Rejecting that argument, the Court held that it was "impossib[le]" for generic manufacturers to honor both their state and federal duties. *Ibid.* Because preemption hinges on "whether the private party could independently do under federal law what

state law requires of it," the plaintiffs' mere "conjectures" would not "suffice to prevent federal and state law from conflicting for Supremacy Clause purposes." 564 U.S. at 621. In other words, the preemption analysis "should not involve speculation about ways in which federal agencies and third-party actions could potentially reconcile federal duties with conflicting state duties." *Id.* at 623 (plurality op.).

This Court applied the above preemption principles to design-defect claims in *Mutual Pharmaceutical Co. v. Bartlett*. There, to avoid design-defect liability under New Hampshire law, drug manufacturers had to either design a safer drug or add a stronger warning to the label. 570 U.S. at 482-83. The plaintiff argued that, at the very least, the defendant generic manufacturer could comply with both federal and state law by simply pulling its drug from the New Hampshire market altogether. *Ibid.* The Court disagreed.

Bartlett concluded that accepting the plaintiff's argument would render impossibility preemption "all but meaningless." *Id.* at 488. That is because federal law prevented the generic manufacturer from either redesigning the drug or strengthening the label. And because federal law "prohibited" the "remedial action required to avoid liability" under New Hampshire law, the plaintiff's design-defect claim was preempted. *Id.* at 486. Above all, this Court's "preemption cases presume that an actor seeking to satisfy both his federal and state-law obligations is not required to cease acting altogether in order to avoid liability." *Id.* at 488.

As the record here shows, the FDA rejected the very label Merck needed to avoid state tort liability. And it is the FDA, not the states, that Congress gives the final statutory and regulatory authority to determine a drug's label. But a state-law duty to provide a warning that the FDA has already rejected is a duty to misbrand drugs in violation of federal law. Under these facts, any liability that arises from breaching such a state-law duty is preempted under the Supremacy Clause.

2. In the face of this Court's preemption precedents, the respondents argue that the FDA might have approved a stronger Fosamax warning if only Merck had worded its supplement application differently. The Third Circuit agreed, assuming that a reasonable jury "could find it less than highly probable" that the FDA would have rejected a differently phrased warning about atypical femoral fractures. Pet. App. 56a-57a. According to the appeals court, the "question for preemption purposes is whether the FDA would have approved a different label amendment than the one it actually rejected in the May 2009 letter." *Id.* at 52a.

But Merck's PAS submission must be viewed "in its entirety, not distorted as an exercise in disjointed parsing." *In re Sawyer*, 360 U.S. 622, 653 (1959) (Frankfurter, J., dissenting). That is, "[w]e must think things, not words, or at least we must constantly translate our words into facts for which they stand, if we are to keep to the real and the true." Oliver Wendell Holmes, Jr., *Law in Science and Science in Law*, 12 Harv. L. Rev. 443, 460 (1889). Here, the FDA's outright rejection of Merck's label supplement with no haggling over its wording

shows that the FDA believed *no* additional warning was appropriate at that time.

And contrary to the respondents' claim, nothing in *Levine* "impos[es] upon [a] drug manufacturer a duty to continually 'press' an enhanced warning which has been rejected by the FDA." *Dobbs v. Wyeth Phram.*, 797 F. Supp. 2d 1264, 1279 (W.D. Okla. 2011). In all events, the relevant question for preemption purposes isn't whether Merck could have asked for a differently worded warning, but whether the FDA would have approved one. *Levine*, 555 U.S. at 618-20. On that crucial point, there is no need for guesswork.

"If a warning is warranted, FDA will attempt promptly to identify easily corrected deficiencies in the proposed text and will then develop final labeling text with the manufacturer in an iterative process." U.S. Cert. Br. 21; *see* 21 C.F.R. 314.102(b). As the United States has confirmed, and the FDA's Complete Response Letter made clear at the time, the FDA rejected Merck's proposed warning "based on the agency's determination that the data was then insufficient to justify such a warning." U.S. Cert. Br. 22. Allowing a jury to second guess that decision based on semantics "would exert an extraneous pull on the scheme established by Congress." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 353 (2001).

Levine's discussion of the history of Phenergan's label confirms that the Court understood its "clear evidence" standard as one that manufacturers could plausibly meet under an appropriate set of facts. Although the record in

Levine lacked such facts, they are present here—in spades. In contrast, the Third Circuit's rule sets the "clear evidence" bar so high that drug manufacturers can't possibly meet it even with a "smoking gun" rejection letter from the FDA. Pet. App. 55a.

If a plaintiff's counterfactual speculation about alternative wording can defeat impossibility preemption, brand-name drug manufacturers will leave nothing to chance. They will "have an incentive to submit a deluge of information that the [FDA] neither wants nor needs, resulting in additional burdens on the FDA's evaluation" of a label's adequacy. *Buckman*, 531 U.S. at 351. Under such a preemption regime, the FDA will be forced to divert precious time and resources to responding to manufacturers' futile, inexhaustibly worded label-change requests, rather than protecting the public health.

By focusing on what the FDA might have done rather than on what the FDA did, the Third Circuit's rule dilutes *Levine* beyond recognition. If the Court were to adopt this view of conflict preemption, it would render the Supremacy Clause "all but meaningless." *Mensing*, 564 U.S. at 621. At the same time, if the rationale for this Court's holding in *Levine* is to remain viable, the judgment below must be reversed.

B. None of *Levine*'s Case-Specific Barriers to Preemption Apply Here.

Like many conflict-preemption cases, *Levine* turned on its own sui generis facts. In denying preemption to Wyeth, the manufacturer of

Phenergan, the Court stressed that (1) Wyeth never advised the FDA of the dangers of administering Phenergan by the IV-push method; (2) Wyeth never tried to change Phenergan's label to warn of those dangers; (3) scant record evidence suggested that the FDA would have rejected a stronger warning label for Phenergan; and (4) the FDA never rejected a stronger warning. *None* of those fact-bound barriers to preemption exists here.

1. This case differs from *Levine* in many crucial respects. In *Levine*, for example, Wyeth did not even "argue that it supplied the FDA with an evaluation or analysis concerning the specific dangers posed by the IV-push method." 555 U.S. at 572-73. If anything, neither Wyeth nor the FDA "gave more than passing attention to the issue." *Id.* at 563.

Compare that "sparse correspondence," *id.* at 561, with Merck's detailed back-and-forth Merck with the FDA here. After published studies began suggesting a possible link between long-term Fosamax use and atypical femoral fractures, Merck immediately "submitted a comprehensive safety update" to the FDA. Pet. App. 13a-14a. And when the FDA asked Merck for all available information linking the use of bisphosphonates to such fractures, Merck complied fully. *Id.* at 14a.

Unlike in *Levine*, it is "undisputed that the FDA was aware of the possible link between Fosamax and atypical fractures well before September 2010." *Id.* at 60a. Yet because the "conflicting nature of the literature d[id] not provide a clear path forward," the FDA needed "more time"

to consider "the issue of a precaution." *Id.* at 59a-60a.

2. Nothing in *Levine*'s record suggested that Wyeth "had 'earnestly attempted' to strengthen [Phenergan's] intra-arterial injection warning." 555 U.S. at 561. Though Wyeth proposed language to warn of the risks of injecting Phenergan intra-arterially, "the FDA did not regard the proposed warning as substantively different." *Id.* at 573 n.5. In other words, Wyeth's "proposed warning was different, but not stronger." *Ibid.*

At bottom, Wyeth didn't "argue that it attempted to give the kind of warning required by the Vermont jury but was prohibited from doing so by the FDA." *Id.* at 572. For that reason, as the United States has explained, *Levine* "did not resolve how to determine the meaning and effect of an actual FDA labeling-supplement decision" because Wyeth never proposed, and the FDA never rejected, a stronger warning. U.S. Cert. Br. 23.

Not so here. Merck didn't even wait for the FDA to fully analyze the available data before acting. As Merck's PAS submission makes clear, Merck formally asked the FDA for permission to change Fosamax's label in September 2008. Relying on nine articles and an analysis of femoral fractures in Fosamax users, Merck emphasized the importance of "includ[ing] an appropriate statement" on the label to "increase physicians' awareness of possible fractures * * * and [to] allow early intervention." Pet. App. 15a.

In particular, Merck proposed adding, under the Adverse Reactions section of Fosamax's label, "low-energy femoral shaft fracture" as a potential adverse reaction. *Id.* at 16a. Under the Warnings & Precautions section, Merck proposed adding a new subsection entitled "Low-Energy Femoral Shaft Fracture," which warned that "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients." *Id.* at 15a-16a.

As the record shows, Merck did everything in its power to obtain the FDA's approval for a stronger warning label. That fact alone distinguishes this case from *Levine*.

3. *Levine* hinged on the "absen[ce of] clear evidence that the FDA would not have approved a change to Phenergan's label." 555 U.S. at 571. Though Wyeth "suggest[ed] that the FDA intended to prohibit it from strengthening the [label]," it provided little evidence of that intention. As a result, "both the trial court and the Vermont Supreme Court rejected [Wyeth's contention] as a matter of fact." *Id.* at 572.

In contrast here, Merck has adduced ample evidence that the FDA would not approve a change to Fosamax's label. Confronted with Merck's data, FDA made clear that any "[d]iscussion of the risk factors for stress fractures [was] not warranted and [was] not adequately supported by the available literature and post-marketing adverse event reporting." Pet. App 18a-19a. The agency's March 2010 safety announcement reiterated that the available data still had "not shown a clear

connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures." *Id.* at 19a.

And unlike the factfinder in *Levine*, the district court explicitly found that "the FDA would not have approved a change to the Precautions section of the Fosamax label." *Id.* at 168a. Neither the Third Circuit nor the respondents contested any of the "undisputed" facts supporting that finding. *Id.* at 47a.

4. In *Levine*, the FDA "had not made an affirmative decision" to reject a stronger warning for Phenergan. 555 U.S. at 572. The record "lack[ed] any evidence that the FDA set a ceiling on this matter." *Id.* at 561. But here no one disputes that the FDA affirmatively rejected Merck's attempt to strengthen its Fosamax label.

While the FDA agreed that Merck could add "low-energy femoral shaft and subtrochanteric fractures" to the Adverse Reactions section of the label, it expressly rejected Merck's proposed changes to the Warnings & Precautions section. Pet. App. 18a-19a. An FDA liaison instructed Merck to "hold off" on changing the Warnings & Precautions label until the FDA could "decide on language" for a stronger precaution "if it is warranted." *Id.* at 17a-18a. As the district court put it, the record "provide[s] clear evidence that the FDA *would* have rejected a stronger Precautions warning because the FDA *did* reject a stronger Precautions warning." Pet. App. 150a.

Unlike *Levine*, this record leaves no doubt that the FDA both considered and rejected the very

warning that is the basis for the respondents' failure-to-warn claim. That isn't a distinction without a difference; it is a dispositive fact that singlehandedly answers the question presented.

II. No Presumption Against Preemption Applies Here.

In equating *Levine*'s "clear evidence" requirement with a clear-and-convincing-evidence standard of proof, the panel below invoked the "presumption against preemption." Pet. App. 37a (citing *Levine*, 555 U.S. at 571-73, 565 n.3). But that presumption has no bearing here. In fact, as shown below, *no* presumption attaches when deciding whether state law conflicts with federal law.

1. No basis exists in the Constitution for applying a presumption against preemption—in this or any other case. As "a matter of constitutional structure, there should be no systematic presumption against or in favor of preemption." Viet D. Dinh, *Reassessing the Law of Preemption*, 88 Geo. L.J. 2085, 2092 (2000). The Supremacy Clause makes Congress's lawful enactments "the supreme Law of the Land[,] * * * any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const. art. VI, cl. 2.

That concluding phrase—"any Thing in the Constitution or Laws of any State to the Contrary notwithstanding"—is a classic *non obstante* provision. In the 18th century, legislatures used *non obstante* provisions "to specify that they did not want courts distorting the new law to accommodate the old." *Mensing*, 564 U.S. at 621-22 (plurality opinion).

The Supremacy Clause's *non obstante* provision "indicates that a court need look no further than 'the ordinary meanin[g]' of federal law, and should not distort federal law to accommodate conflicting state law." *Id.* at 623 (plurality opinion) (quoting *Levine*, 555 U.S. at 588) (Thomas, J., concurring in judgment). By going beyond the "ordinary meaning," the presumption against preemption distorts federal law. *See* Caleb Nelson, *Preemption*, 86 Va. L. Rev. 225, 304 (2000).

Nor is any such presumption required "to defend state interests from undue infringement." *Geier v. Am. Honda Motor. Co.*, 529 U.S. 861, 907 (2000) (Stevens, J., dissenting). After all, "[i]f a power is delegated to Congress in the Constitution, the Tenth Amendment expressly disclaims any reservation of that power to the States." *New York v. United States*, 505 U.S. 144, 156 (1992). Put differently, the Constitution itself resolves the inherent tension between federal and state power with a straightforward, self-executing rule: federal law trumps conflicting state law.

2. A presumption against preemption is also ahistorical. There is "no significant support in constitutional history for the conclusion that the [F]ramers intended any such presumption to be read into Article VI, clause 2." Martin R. Scordato, *Federal Preemption of State Tort Claims*, 35 U.C. Davis L. Rev. 1, 30 (2001).

On the contrary, the Framers adopted the Supremacy Clause precisely "to remedy one of the chief defects in the Articles of Confederation, by instructing courts to resolve state-federal conflicts in

favor of federal law." David Sloss, *Constitutional Remedies for Statutory Violations*, 89 Iowa L. Rev. 355, 402 (2004). By design, the Supremacy Clause "invalidates" any "interfer[ing]" or "contrary" state law. *Hillsborough Cnty., Fla. v. Automated Med Labs., Inc.*, 471 U.S. 707, 712 (1985) (internal citations and quotations omitted).

Nor does the presumption against preemption enjoy a long pedigree. *See, e.g.*, Mary J. Davis, *Unmasking the Presumption in Favor of Preemption*, 53 S.C. L. Rev. 967, 974 (2002) (showing that the Court's earlier preemption cases "resulted in almost automatic preemption of concurrent state regulation"). On the contrary, it wasn't until the 1980s that the presumption first arose in field preemption cases "as a possible reaction to the [federal government's] significant and ever-widening control over so many aspects of our daily lives." *Id.* at 1013. But for most of its history, "the Court has consistently applied implied preemption doctrine broadly to support a finding of preemption." *Ibid.*

3. Nothing in logic supports a presumption against preemption in cases—such as this one—where preemption hinges on the existence of a conflict between state and federal law. Instead, every reason exists to presume that Congress always wishes to preempt state law that conflicts with federal law. "Why," after all, "would Congress not have wanted ordinary pre-emption principles to apply where an actual conflict with a federal objective is at stake?" *Geier*, 529 U.S. at 870. If courts must presume otherwise, "state law could impose legal duties that would conflict directly with

federal regulatory mandates." *Ibid.* That can't be right.

This Court has recently abolished any "presumption against preemption" in express-preemption cases. In *Puerto Rico v. Franklin-California-Tax-Free Trust*, the Court held that when a "statute 'contains an express pre-emption clause,' we do not invoke any presumption against pre-emption." 136 S. Ct. 1938, 1946 (2016) (quoting *Chamber of Commerce of the United States v. Whiting*, 563 U.S. 582, 594 (2011)). Instead, the Court simply "'focus[es] on the plain wording of the clause, which necessarily contains the best evidence of Congress' pre-emptive intent.'" *Ibid.*

But a presumption against preemption makes even less sense in conflict-preemption cases. Perhaps that is why the Court has openly questioned whether the presumption should ever apply in conflict-preemption cases. *See, e.g., Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 374 n.8 (2000) ("We leave for another day a consideration in this [implied preemption] context of a presumption against preemption."); *United States v. Locke*, 529 U.S. 89, 108 (2000) ("No artificial presumption [against preemption] aids us."). And some members of the Court have already answered "no." *See, e.g., Mensing*, 564 U.S. at 622 (Thomas, J.) (plurality opinion) (explaining that, if anything, "federal law should be understood to impliedly repeal conflicting state law").

Conflict preemption is the quintessential example of the Supremacy Clause at work. When a true federal-state conflict exists, preemption is

"inescapable and requires no inquiry into congressional design." *Fla. Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963). That is because "*any* state law, however clearly within a State's acknowledged power, which interferes with or is contrary to federal law, must yield." *Felder v. Casey*, 487 U.S. 131, 138 (1988) (emphasis added); *Fidelity Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982) ("[S]tate law is nullified to the extent that it actually conflicts with federal law.").

Under the Supremacy Clause, "the relative importance to the State of its own law is not material when there is a conflict with a valid federal law." *Ibid.* (internal citations and quotations omitted). And because the scope of the conflict itself delineates the scope of preemption, "a narrow focus on Congress's intent to supersede state law is misdirected." *City of New York v. FCC*, 486 U.S. 57, 64 (1988).

As the Eleventh Circuit has noted, "it is difficult to understand what a presumption in conflict preemption cases amounts to, as we are surely not requiring Congress to state expressly that a given state law is preempted using some formula or magic words." *Fla. State Conference of the NAACP v. Browning*, 522 F.3d 1153, 1168 (11th Cir. 2008). Nor is federal law "obliged to bend over backwards to accommodate contradictory state laws, as should be clear from the Supremacy Clause's blanket instruction." *Ibid.*

4. Even when the Court has applied the presumption against preemption, it has done so

inconsistently. True, in many cases when the Court's majority finds no preemption, it will invoke the presumption. *See, e.g., Bates v. Dow Agrosciences LLC*, 544 U.S. 431 (2005) (finding that federal law regulating pesticides doesn't preempt state statutory and common-law claims); *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996) (finding that the FDCA's manufacturing and labeling requirements for medical devices don't preempt state common-law claims).

But just as often, when the Court finds state law preempted, the presumption vanishes without a trace. *See, e.g., Arizona v. United States*, 567 U.S. 387 (2012) (preempting Arizona's efforts at cooperative enforcement of federal immigration law); *Riegel v. Medtronic, Inc.*, 552 U.S. 312 (2008) (preempting New York's common-law claims under the FDCA); *Geier*, 529 U.S. at 906-07 (Stevens, J., dissenting) ("[T]he Court simply ignores the presumption [against preemption].").

In other words, the Court "continues to simultaneously repeat and ignore the presumption against preemption." Calvin R. Massey, *Joltin' Joe Has Left and Gone Away: The Vanishing Presumption Against Preemption*, 66 Alb. L. Rev. 759, 764 (2003). But a legal presumption the Court can wield or withold as it pleases is little more than a crude parlor trick. It is like preening before a funhouse mirror; what you see depends on where you stand. Above all, "the maintenance of a presumption against preemption" forces the Court "to treat essentially similar cases in very different manners." Scordato, *supra*, at 30-31.

What's more, the Court's invocation of the presumption has become increasingly erratic in recent years. For example, among the five preemption cases decided during the 2011 Term, *none* discussed the presumption against preemption. *See* Ernest A. Young, *"The Ordinary Diet of the Law": The Presumption Against Preemption in the Roberts Court*, 2011 Sup. Ct. Rev. 253, 331 (2012). Armed with so pliable a presumption, the Court can hardly help but act capriciously. And to the extent the Court "systematically favor[s] one result over another" when analyzing state and federal conflicts, it "risk[s] an illegitimate expansion of the judicial function." Dinh, *supra*, at 2092.

* * *

The Supremacy Clause speaks for itself. The Court "should not strain to find ways to reconcile federal law with seemingly conflicting state law." *Mensing*, 564 U.S. at 622. The petitioner deserves to have its preemption defense evaluated on the best available evidence of an actual conflict rather than on a presumption that bears no apparent relation to that question. As it has done many times before, this Court should apply "ordinary," "longstanding," and "experience-proved principles of conflict preemption." *Geier*, 529 U.S. at 874. That analysis should be based on the substantive requirements of state and federal law—*not* on the expedient of some *a priori* rule of decision.

CONCLUSION

The Court should reverse the judgment below.

Respectfully submitted,

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